DECEMBER 1953

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

POLIOMYELITIS: ITS CONTROL AND PREVENTION

A Symposium

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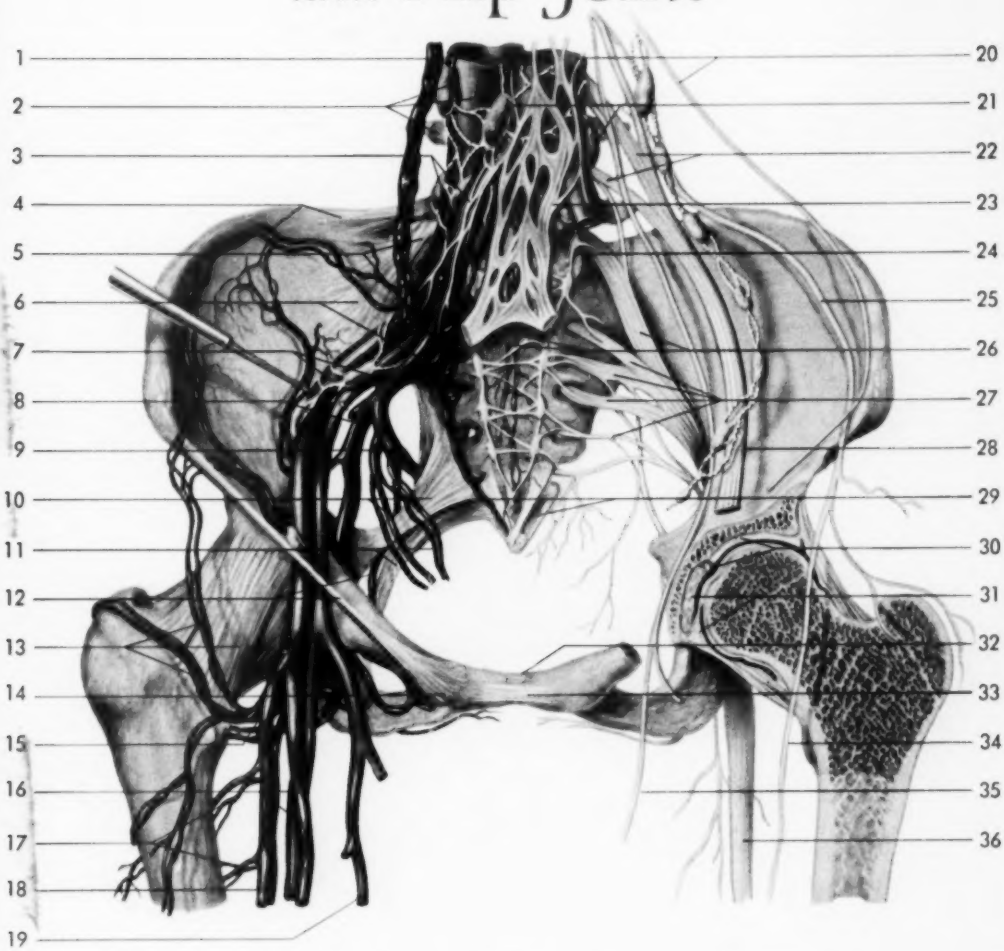

1 Ovarian artery and vein
2 Vena cava; lumbar lymph nodes
3 Right common iliac artery and vein
4 Iliolumbar ligament; branches of iliolumbar artery and vein
5 Lumbosacral ligament; superior gluteal artery and vein
6 Anterior sacroiliac ligament; internal iliac (hypogastric) artery
7 External iliac artery and vein
8 Obturator artery and vein
9 Inferior gluteal artery and vein
10 Sacrospinous ligament; uterine artery and vein
11 Sacrotuberous ligament; vaginal artery and vein
12 Inguinal ligament; internal pudendal artery
13 Iliofemoral ligament; branches of lateral femoral circumflex artery and vein
14 Lacunar ligament
15 Lateral femoral circumflex artery and vein
16 Femoral artery and vein
17 Perforating arteries and veins
18 Deep femoral artery and vein
19 Great saphenous vein
20 Aorta; ilioinguinal nerve
21 Lateral aortic lymph nodes
22 Lumbar nerves
23 Hypogastric sympathetic plexus
24 Sympathetic trunk
25 Lateral femoral cutaneous nerve
26 Middle sacral artery and vein; lumbosacral trunk
27 Sacral nerves
28 Femoral nerve
29 Lateral sacral artery and vein; anterior sacrococcygeal ligament
30 Lunate articular cartilage; joint cavity
31 Acetabular fat pad; ligamentum teres
32 Interpubic fibrocartilage
33 Superior pubic ligament
34 Anterior branch of lateral femoral cutaneous nerve
35 Obturator nerve
36 Great sciatic nerve

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*Yow, E. M.: *Am. Pract.*, 4:521 (Aug.) 1953.

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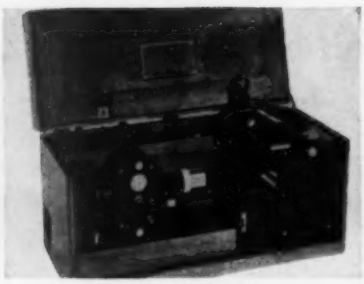

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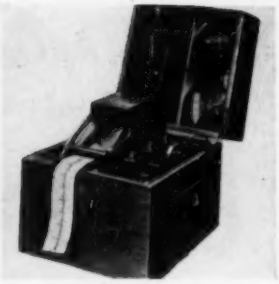

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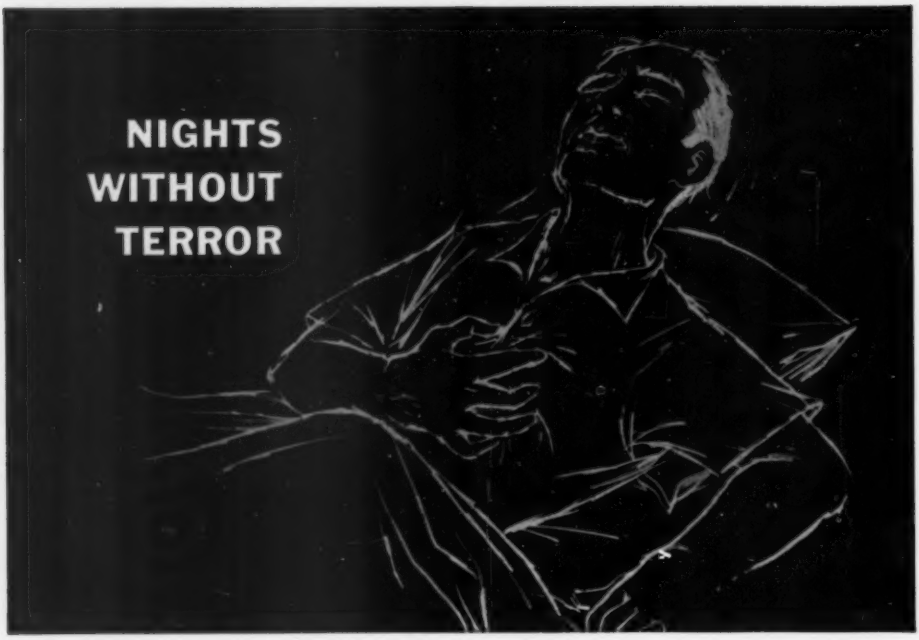

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1. Humphreys, P., et al.: Angiology 3:1 (Feb.) 1952.
2. Plotz, M.: New York State J. Med. 52:2012 (Aug. 15) 1952.
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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 29, NO. 12 DECEMBER 1953

POLIOMYELITIS: ITS CONTROL AND PREVENTION*

A Symposium

HERMANN M. BIGGS MEMORIAL LECTURE†

The Epidemiology and Pathogenesis of Poliomyelitis

DOROTHY M. HORSTMANN

Passive Immunization against Poliomyelitis with Especial Consideration of the Effectiveness of Gamma Globulin

W. McD. HAMMON

Active Immunization against Poliomyelitis

HERALD R. COX, SC.D.

* Presented at the Stated Meeting of The New York Academy of Medicine, April 2, 1953.
† Under the auspices of the Committee on Public Health Relations.

THE EPIDEMIOLOGY AND PATHOGENESIS OF POLIOMYELITIS*

DOROTHY M. HORSTMANN†
Associate Professor of Preventive Medicine, Yale University School of Medicine, New Haven, Conn.

IN approaching the problems of the prevention and control of poliomyelitis, the epidemiology and pathogenesis of the disease assume basic importance, and it is these aspects about which I shall speak tonight. Since they are both vast subjects I can only hope to cover certain recent developments which are of particular interest.

As far as the epidemiology is concerned, the picture is ever a changing one, both in the behavior of the disease and in the interpretations which investigators place upon it. Remarkable reversals of opinion have occurred in the past twenty years; these were summarized by Dr. Paul[1] at the recent 2nd International Poliomyelitis Congress as follows:

"A disease originally regarded as being limited to infants is now no longer confined to infancy. A disease originally considered as mildly contagious is now regarded as *very* contagious—almost as much so as measles. A disease in which the clinical picture was originally thought to be limited to acute paralysis now is regarded as a disease in which only one in a hundred or more of those infected become paralyzed—and if the Lansing strain is involved, perhaps one in a thousand. From an endemic disease it has tended to become epidemic and is now a common and periodic scourge, and incidentally, an item of great public interest."

It is generally agreed, today, that poliomyelitis is spread primarily by human association. But the situation is complicated in that there seem to be a number of conditioning factors which come into play. To begin with there is the problem of the seasonal incidence of the disease: no one has satisfactorily explained the curious concentration of cases which occurs in the summer and early fall. Two likely factors are: 1) enormously increased dissemination of the virus in the community at

* From the Section of Preventive Medicine Yale University School of Medicine, New Haven, Conn. Aided by a grant from the National Foundation for Infantile Paralysis.
† Presented by invitation at the Stated Meeting of The New York Academy of Medicine in the Symposium on Poliomyelitis: Its Control and Prevention, April 2, 1953. Manuscript received May 1953.

these times; and 2) markedly decreased resistance on the part of the host. The evidence to date, gathered from several types of studies, favors the former possibility. Thus Trask and Paul[2] and Melnick[3] by examining sewage from a certain area in New York City, monthly for six years, found that virus, presumably derived from the only known reservoir, man, could be isolated fairly regularly from sewage samples in the late summer and early fall but not during the rest of the year. Turner's serological studies in Baltimore,[4] covering a period of five years, show that antibodies to Type 2 poliomyelitis virus are not acquired uniformly throughout the year, but are acquired by children only during the summer time, i.e., exactly the same season at which clinical cases of poliomyelitis occur in this area. Thus it would seem that something facilitates the spread of poliomyelitis virus during the summer. The possibility exists that flies, which are known to harbor the virus in epidemic areas, are important in disseminating it under certain circumstances, but the exact relationship between infected flies and infected people has not been defined, and the reasons for the seasonal incidence of poliomyelitis remain remarkably obscure.

Another obscure feature is the variability of clinical manifestations of poliomyelitis infection, covering the range from completely inapparent on the one hand, to fulminant paralysis and death on the other. What factors are involved here? Such things as dosage and strain must play a role, as well as host factors such as age, physiological state, undue exercise and trauma, etc. The ratio of inapparent infections to clinical cases is a basic concept in understanding the epidemiology of poliomyelitis. Dr. Paul and Dr. Trask referred to the situation as rather akin to an iceberg, in that a few infections are seen above the surface: these are the paralytic and nonparalytic ones; but a far greater number remain completely hidden, and these are the silent, inapparent infections. The ratio of apparent to inapparent is variously given as 1:8 to 1:100 or more; probably it varies not only with the virus type and strain, but with the epidemiological circumstances. Francis[5] believes that the virus is *not* distributed widely and indiscriminately during epidemics, in this country at least. He points to the numerous studies in which a comparison between the number of virus isolations from familial contacts of cases, from nonfamilial contacts, and from those with no known contact have been made. Invariably, the infection rate has been considerably higher in families in which a clinical case has occurred; in one study[6]

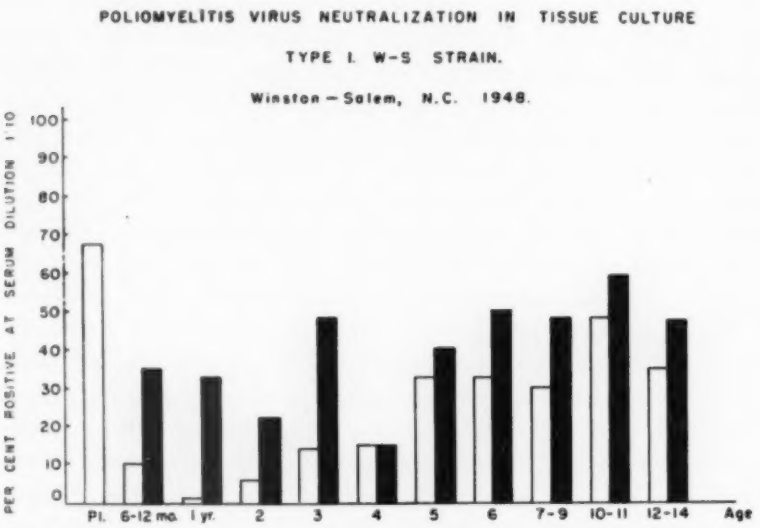

Fig. 1. Pre- and post-epidemic antibody response of normal children in different age groups to Type 1 poliomyelitis virus (epidemic strain). White columns indicate pre-epidemic results; black columns, post-epidemic. Pl. indicates placental serum. (From Melnick and Ledinko,[8] *Amer. J. Hyg. 58*:207-22, 1953. Reprinted by permission.)

it was 75 per cent as compared to 18 per cent in non-contact families, and very low (1.6 per cent) in those families with no known contact. These results, however, may be interpreted as meaning that poliomyelitis is, in part at least, a "place" disease, and the high incidence of infection in certain families may be related to a common source of virus in the environment.[7] To complete the picture, it would be helpful to have serological data on the various family groups to supplement the virus studies, since antibody tests are much more sensitive in detecting evidence of infection than are tests for virus. In any event, it is apparent that during an epidemic, virus is widespread in a community, even if it is more concentrated in some areas than others. Thus during the 1948 outbreak in Winston-Salem, N. C., Melnick and Ledinko[8] have been able to show by serological means, that some 25 per cent of 250 children who remained apparently well throughout the summer, nevertheless became infected with and acquired antibodies to the Type 1 epidemic strain. Figure 1 compares the per cent in each age group which was positive for

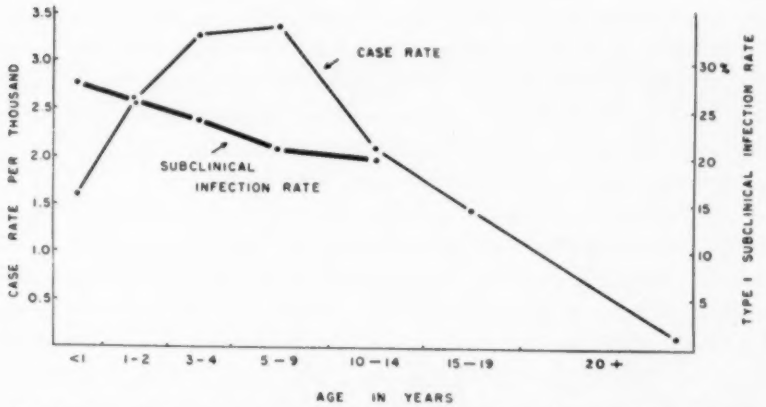

Fig. 2. Comparison of age specific subclinical infection rates per 100, with age specific case rates per 1000, North Carolina, 1948 (From Melnick and Ledinko,[8] *Amer. J. Hyg. 58*:207-22, 1953. Reprinted by permission.)

Type 1 neutralizing antibodies at the beginning of the epidemic, with the per cent positive several months later when the epidemic was over. A considerable shift from negative to positive occurred, particularly in the youngest age group. A similar shift but to a lesser degree, occurred from negative to positive for Type 2 antibodies, although Type 2 virus was not isolated during this epidemic. The antibodies to Type 3, however, remained stationary, indicating that this type was not active in Winston-Salem during the summer of 1948.

These data on inapparent infection rates in the different age groups add considerable information to the old problem of age in reference to susceptibility to paralytic infection. Sabin[9] and Burnet,[10] and others, have maintained that the inapparent infection rate is higher in the infant than in the older child; or, conversely, the older child is more susceptible to paralysis than the younger one. Figure 2, from the above study by Melnick and Ledinko,[8] compares the *age specific infection rate* as measured by antibody determinations, in terms of infections per 100 population, with the *age specific attack rate* per 1000 population in the North Carolina 1948 epidemic. The inapparent infection rate was highest in the very youngest age group, six months to one year, and fell steadily thereafter. In contrast, the attack rate of the disease in this particular epidemic, increased from the age of one to four, reached a peak in

the five to nine age group, and then gradually fell. Whether this is a direct effect of age or an indirect one, it is not possible to say. Conceivably, factors such as exposure, dosage, as well as physical exertion may enter the picture. This latter factor has been shown by Russell[11] in England, and by us in this country,[12] to be related to the severity of the ultimate paralysis, i.e., continued physical activity and stress around the time of onset being associated with a higher incidence of paralysis.

An impressive change which has occurred in the epidemiology of poliomyelitis is the shift in age incidence, so that in certain countries, notably Australia, the Scandinavian countries, and the United States, poliomyelitis is no longer an infantile disease, but one which has increasingly affected older children and young adults. A remarkable thing about the shift in age incidence is that it has not occurred everywhere: poliomyelitis is still an infantile disease in Cuba, in Panama, in Israel, three places where epidemics have occurred recently, as well as in certain countries like Egypt, where no epidemics occur in the native population, and only sporadic cases are seen each year. What has caused this change to occur in some parts of the world, and not in others? The explanation is not simple; but it has been suggested by a number of investigators that in part, the change is related to changes in our 20th Century way of life,—to modern hygiene, to the changing character and composition of the population and curtailment in the size of families. Improved sanitation and the high standards of living in our society seem to protect children from exposure to poliomyelitis virus early in life, postponing the eventual exposure rather than eliminating it. Thus the age at which the clinical attack occurs is ever increasing, and since, like other virus infections, poliomyelitis is more severe and carries a higher mortality in older age groups, it becomes a question as to whether the present state of affairs is wholly desirable.

Results of serological surveys carried out in various parts of the world by Hammon et al.,[13] by Paul, Melnick, and Riordan,[14] and others, tend to support this hypothesis. Thus in Egypt, where Dr. Paul conducted a study, it was found that the population acquires antibodies to all three types of poliomyelitis at a very early age.[15] In Figure 3, the per cent in each age group possessing antibodies to Type 2 poliomyelitis virus is shown. For neutralizing antibodies, the curve indicates that after a loss of maternal antibodies in the first months of life, exposure and infection occur rapidly, and at fourteen months of age, 50 per cent of

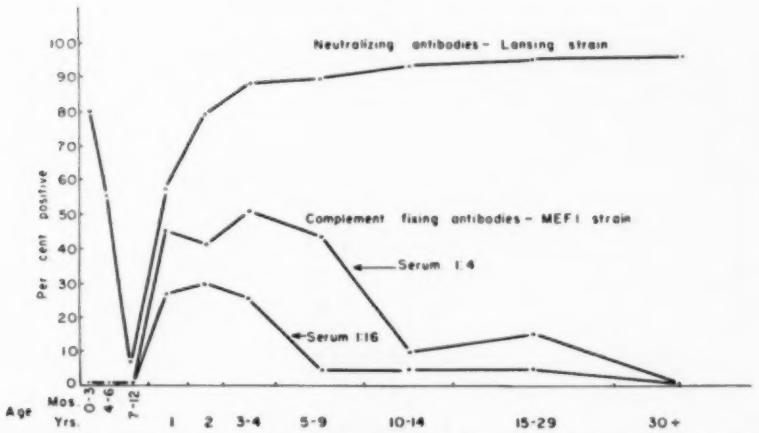

Fig. 3. Antibody responses to Type 2 poliomyelitis virus in a normal population in Egypt. Graph illustrating the per cent of individuals in each age group possessing neutralizing and C-F antibodies. (From Goldblum and Melnick,[18] *Journal of Experimental Medicine*, *96*:175-85, 1952. Reprinted by permission.)

Egyptian children already have antibodies to Type 2 virus. Similar antibody tests with the other 2 types of poliomyelitis virus indicate that by the age of three to four years 75-100 per cent have antibodies to all 3 types. Egypt is a country in which living conditions are crowded, families are large, sanitation is primitive. No epidemics of poliomyelitis occur, presumably because, as has been pointed out by Sabin,[16] by Gear,[17] by Paul,[15] and others, exposure at an early age is so great that the entire population is infected and already immune by the age of three to four years. In this process, a certain number of paralytic cases occur, all in the zero to four age group, but these are probably few compared to the number infected. This interpretation is supported by the observations of Goldblum and Melnick[18] on the development of complement fixing antibodies to Type 2 poliomyelitis virus in this same population. The C-F antibody, unlike the neutralizing one, is transient and persists for only a few years. Unlike the neutralizing antibody it was not present in Egyptian babies at birth as a result of passive transfer from maternal blood, but appeared early in life and was in fact present in significant titer only in young children, those under five years of age (Fig. 3). This is confirmatory evidence that recent infections are confined to this

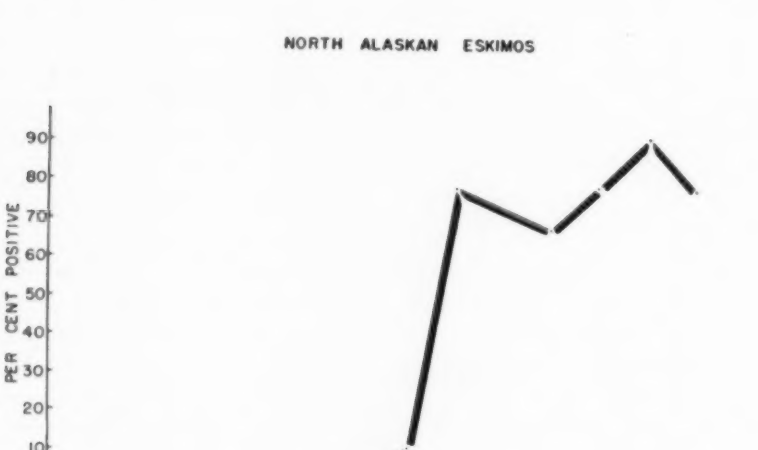

Fig. 4. Type 2 poliomyelitis neutralizing antibody pattern of North Alaskan Eskimos, by age groups. (From Paul, J. R. *Trans. Assoc. Amer. Physns. 65*:184-90, 1952. Reprinted by permission.)

young age group in this population.

In complete contrast to the situation in Egypt is the one in Northern Alaska where Dr. Paul also carried out a similar serological study.[19] In two Eskimo villages, which were remote in location, the epidemiological situation is just the opposite to that in crowded Cairo, and here the antibody patterns are also completely different: virtually none of the individuals under twenty years of age were found to have Type 2 neutralizing antibodies, while sera from almost all individuals over twenty were positive for this antibody (Fig. 4). This reflects the fact that the last recorded epidemic of poliomyelitis in the area occurred twenty years previously, in 1930. Apparently in this remote northern land, the infection swept through the population in 1930, paralyzing a few and immunizing many, and then died out; thus no one born since the 1930 epidemic had acquired antibodies. Antibody studies on the prevalence of the other 2 types of poliomyelitis virus in the same population indicated that these had been present even earlier than Type 2, for only individuals thirty-five years of age and over had Type 1 antibodies, and only those forty-five and over had antibodies to Type 3. Apparently

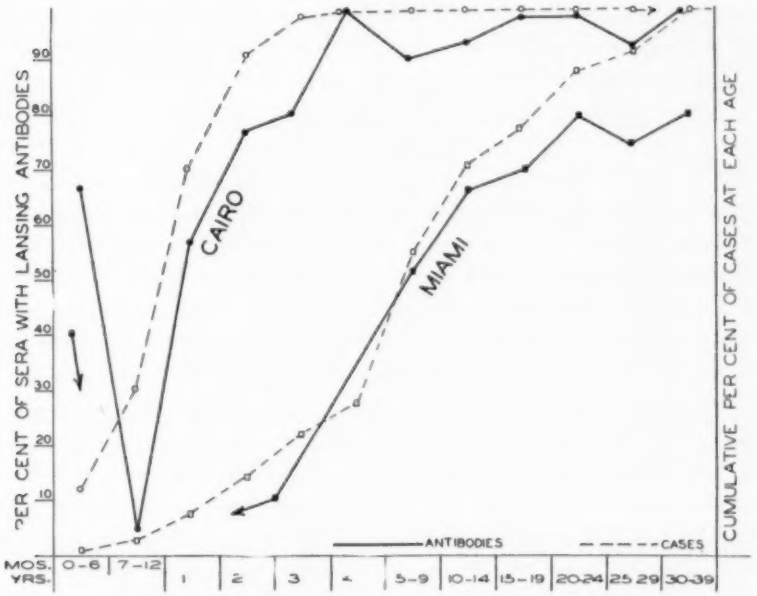

Fig. 5. Comparison of Type 2 neutralizing antibody pattern with cumulative attack rate of poliomyelitis in two subtropical areas. (From data of Paul, Melnick, and Riordan.[15])

neither of these types had reappeared since their visitations in the early part of the century.

Although the Lansing Type 2 is only one of the 3 types, and never has been known to cause an epidemic, it has turned out that Lansing virus is widespread in the world, and Type 2 antibodies are a good index of immunity to poliomyelitis in general in a given population; for the age at which Lansing antibodies are acquired parallels the age at which clinical poliomyelitis appears in most populations studied. Figure 5 compares the age at which Type 2 antibodies appear with the curve for the cumulative per cent of cases indicating the age at which clinical poliomyelitis appears, in two different populations. Thus in Cairo, where antibodies appear very early, so does the clinical disease. On the other hand in Miami, Florida which happens to be in the same geographical latitude as Cairo, Lansing antibodies appear much more

slowly, and not until five to nine years of age have 50 per cent of the children acquired them. Correspondingly, the age at which clinical poliomyelitis develops is also older than in Cairo children; only 14 per cent of the total cases occur in the zero to two year olds (for Cairo it is 91 per cent) and only 70 per cent under the age of fifteen.

These data in terms of the changing age distribution of poliomyelitis in certain parts of the world, support the hypothesis mentioned earlier, namely that in populations living under primitive sanitary conditions where exposure to poliomyelitis virus occurs early in life, infection and antibodies appear at an early age, and consequently the disease remains endemic, in the form of old fashioned "infantile paralysis." In contrast, in populations with high standards of living, in which the infants and young children are protected from exposure to poliomyelitis virus, infection is delayed, antibodies appear slowly, epidemics occur when virus is introduced into a community with a large number of susceptibles, and the age at which the clinical disease develops is ever greater. That the difference in two such populations as Cairo and Miami is related to socio-economic conditions–primitive standards of sanitation and crowding–is brought out by studies by Hammon et al.[13] and by Melnick and Ledinko,[20] which show that different patterns can be found within the same city, by comparing the results with upper and lower socio-economic groups.

Now having merely touched on a few of the problems of the epidemiology of poliomyelitis, I shall leave this subject, and turn to a consideration of the pathogenesis of the disease. As with many other aspects of poliomyelitis, the pendulum of opinion of investigators has swung back and forth from one extreme to another in the last fifty years. The issue has been whether poliomyelitis is a strictly neurotropic agent, or whether there is a primary non-neural development, and possibly a blood phase. The earliest workers, Wickman and others, believed that poliomyelitis had a "systemic," "general," extra-nervous stage preceding invasion of the CNS by some days. In 1912, Peabody, Draper and Dochez,[21] and in 1917 Draper alone,[22] emphasized this concept and pointed to the biphasic course of the clinical disease as evidence: the first or systemic phase being associated with non-specific symptoms,–fever, sore throat, gastrointestinal symptoms; then a period of remission, which marks the end of the disease in most cases, but is followed in some by the second or central nervous system phase, in which neurological signs

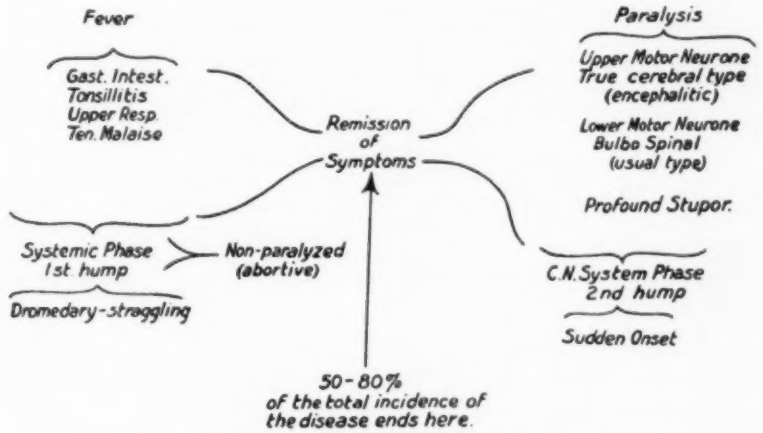

Fig. 6. Draper's analysis of the "dromedary" or biphasic course in human poliomyelitis in terms of a systemic 1st phase and a CNS 2nd phase. (From Draper,[22] *Acute Poliomyelitis*. Philadelphia, Blakiston, 1917. Reprinted by permission.)

appear (Fig. 6). This interpretation of the pathogenesis of poliomyelitis was not seriously challenged until the 1930's, when Flexner,[23] and Faber,[24] and others developed the thesis that the virus of poliomyelitis is strictly neurotropic, and in the human infection it travels along the neural pathway of the olfactory tract to reach the CNS. However, this concept was short-lived. The nasal portal of entry as the sole neural pathway was discarded in the late 1930's with the demonstration by Sabin and Ward[25] that in the human disease neither lesions nor virus could be demonstrated in the olfactory apparatus, whereas Sabin and Olitsky[26] had shown that there are characteristic lesions in the olfactory bulbs in monkeys infected by the instillation of virus into the nostrils. Furthermore, the detection of virus in the stools by Harmon,[27] by Trask, Vignec and Paul,[28] and others, the finding of virus in various parts of the intestinal tract by Sabin and Ward,[25] and Kessel et al.,[29]—these observations caused a reorientation in thinking about the pathogenesis of poliomyelitis, and the possibility of extraneural multiplication of the virus, in the wall of the intestinal tract, for instance, loomed large. Subsequently, the growth of virus in vitro by Enders, Weller and Robbins,[30] and others,—in skin, muscle, testis, and other non-neural tissues, again cast doubt on the strict neurotropism of poliomyelitis virus.

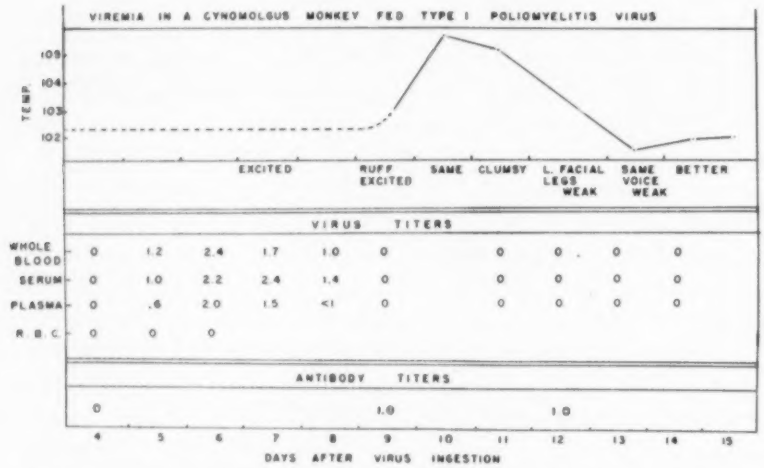
VIREMIA IN A CYNOMOLGUS MONKEY FED TYPE I POLIOMYELITIS VIRUS
TEMP.
109
104
103
102
EXCITED
RUFF EXCITED
SAME
CLUMSY
L. FACIAL LEGS WEAK
SAME VOICE WEAK
BETTER
VIRUS TITERS
WHOLE BLOOD 0 1.2 2.4 1.7 1.0 0 0 0 0 0
SERUM 0 1.0 2.2 2.4 1.4 0 0 0 0 0
PLASMA 0 .6 2.0 1.5 <1 0 0 0 0 0
R. B. C. 0 0 0
ANTIBODY TITERS
0 1.0 1.0
4 5 6 7 8 9 10 11 12 13 14 15
DAYS AFTER VIRUS INGESTION

Fig. 7. Viremia during the incubation period in a cynomolgus monkey paralyzed after ingestion of poliomyelitis virus.

The question as to whether or not viremia occurs entered into the problem of the pathogenesis of the disease from the beginning. Draper and others believed as early as 1917 that the virus was in the blood during the systemic infection phase, and only when it penetrated the "blood-brain barrier" did disease of the CNS occur. A difficulty was encountered, however, in that the search for virus in the blood of patients during the years 1909 to 1914 yielded only negative results. It was not until some years later, in 1943, when a single isolation of poliomyelitis virus from the blood of a child with abortive poliomyelitis was made by Drs. Ward, Melnick and myself.[31] At the time, we thought it a rare occurrence and of no significance in the pathogenesis of the disease. However, when it was shown subsequently by Hammon and Roberts[32] and Steigman and Sabin[33] that antibodies are already present at the time of onset of CNS signs, it seemed likely that if viremia occurs in the human infection, it does so early, in the incubation period or minor illness phase. In other words, the negative results with human blood may have been due to the fact that the search had been made too late in the course of infection. The problem was therefore first attacked experimentally in cynomolgus monkeys and chimpanzees following infection by a natural route, i.e., orally. It had been established by von

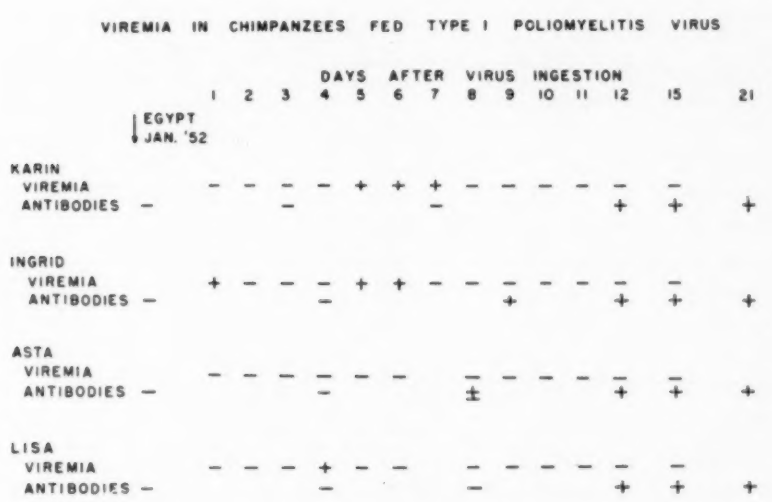

Fig. 8. Heterologous challenge of 4 chimpanzees which had been infected orally with Type 2 poliomyelitis virus 2 months earlier. Karin and Ingrid had also had viremia with their earlier Type 2 infection.

Magnus and Melnick[34] that antibodies develop rapidly after oral infection of monkeys; as in the human disease, they were already found in high titer at the onset of paralysis, which suggested an early phase of viral multiplication outside of the CNS. In a series of experiments in our laboratory, animals were fed virus on one occasion only; beginning twenty-four hours later they were bled daily for five to fifteen days, and the blood specimens were subsequently tested for the presence of poliomyelitis virus.

In the first experiments with cynomolgus monkeys, it was found that with both Type 2 (Y-SK strain) and Type 1 (Egypt strain), viremia appeared with some regularity—usually between the fourth and eighth days after virus ingestion. This was as long as six days before the appearance of paralysis in some of the monkeys.[35] Figure 7 shows the results in one animal which was fed virus and developed fever and neurological signs ten days later. Beginning on the fifth day and continuing through the eighth day, virus was detected in its blood in titers of 10^{-1} and 10^{-2}. No significant difference in titer was noted when whole blood, serum, and plasma concentrations were compared, but no virus was

Name	*Age*	*"Minor Illness" Date Onset Symptoms*	*Date Specimens Collected*	*Results of Virus Tests*			*Antibodies In Blood*
				Throat	*Rectal*	*Blood*	
Barbara W.	10	June 20, 1952	June 23, 1952	+	+	+	
Wanda W.	4	" 22	" "	+	+	+	
David W.	3	" 21	" "	+	+	+	
Bessie W.	2	Asymptomatic	" "	+	+	+	
Neal A.	10 Mos.	June 14	21	+	+	+	
Cathy S.	3	Asymptomatic	July 7	+	+	—	—
Don S.	7	June 19	June 21	+	+	—	—
John K.	3	" 26	" 30	+	+	—	—
Melvin W.	3	Asymptomatic	July 11	+	—	—	—
Dennis J.	11 Mos.	June 2	June 20	+	+	—	+
Kenneth A.	3	" 13	" 21	+	+	—	+
Galen O.	2	Asymptomatic	July 3	—	+	—	+
Barbara R.	6	June 14	June 27	—	+	—	+
Gregg H.	3	July 4	July 11	—	+	—	+
Charles W.	2	Asymptomatic	" 11	+	—	—	+

Fig. 9. The isolation of Type 1 poliomyelitis virus from contacts of cases in an epidemic in Ohio, 1952.

found in the washed red cell fraction. On the ninth day, viremia disappeared, and antibodies were present. Similar results in terms of viremia and the development of antibodies were obtained when virus was introduced into the skin of cynomolgus monkeys.

In chimpanzees fed the Y-SK strain, viremia was shown in three of four animals, four to six days after virus ingestion, and all four developed antibodies. As usual with chimpanzees, none developed paralysis or any other signs of disease. The same four animals, as shown in Figure 8, when fed a heterologous type, Type 1, Egypt strain, two months after their first virus exposure, again developed viremia on the third to sixth days, and in one it was present twenty-four hours after virus ingestion. Again all four developed antibodies early in the course of infection, between the eighth and twelfth days. These results are in agreement with those of Bodian,[36] who has also detected viremia and early antibody formation in orally infected monkeys and chimpanzees.

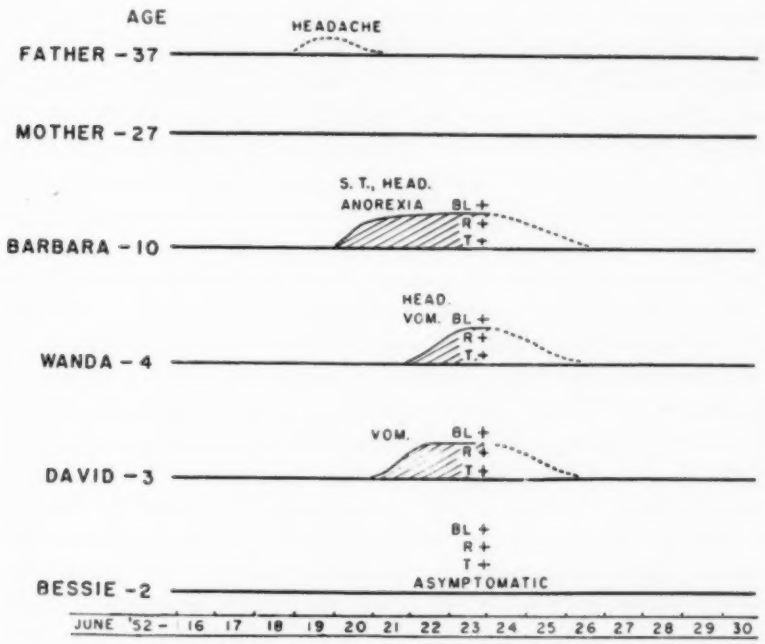

Fig. 10. Diagram of a family outbreak of poliomyelitis in which three cases of the minor illness occurred. Shaded areas indicate period of fever. S. T., sore throat; head., headache; vom., vomiting. + refers to results of tests for virus in blood (B1), rectal swabs (R), and throat swabs (T). (From Horstmann and McCollum,[37] *Proc. Soc. exp. Biol. Med. 82*:434-37, 1953. Reprinted by permission.)

With these experimental results as a background, the problem of viremia in human poliomyelitis was reinvestigated. Dr. Robert McCollum, of the Section of Preventive Medicine, Yale University, collaborated in this phase of the work. Efforts were concentrated on obtaining blood from contacts of cases, who might be in the incubation period, and from children with the minor illness syndrome in the midst of an epidemic. To achieve this, blood specimens, rectal swabs, and throat swabs were collected from some 130 such individuals during an epidemic in Ohio, in June and July, 1952. These were subsequently tested for the presence of poliomyelitis virus, and Figure 9 shows the results with fifteen individuals from whom Type 1 virus has been isolated to date from the throat and/or rectal swabs. Some had symptoms suggestive of the

minor illness, while others remained asymptomatic. Five of the fifteen were found to have virus in the blood, whereas ten of the blood specimens were negative, but six of the negative specimens already had antibodies to Type 1 poliomyelitis virus. Four of the positive results were obtained with blood specimens from four children in the same family, the W family, which was seen during an outbreak of minor illnesses which affected three of the four children.[37] The three older children, aged ten, four, and three, had slight fever, headache, sore throat, anorexia, and vomiting in various combinations. Type 1 poliomyelitis virus was isolated from the blood, throat and rectal swabs of all four children, from the asymptomatic child as well as from the three with symptoms (Fig. 10). The fifth child from whose blood, throat swab, and rectal swab, virus was isolated was a ten month old infant who was asymptomatic on June 21, at the time that the specimens were collected, although he had had a "cold," consisting of cough and rhinitis for the previous week. Three days after the specimen was taken, he developed fever, drowsiness, and some vomiting. These continued for three days and on June 27 he was admitted to the hospital. The physical examination on admission was essentially negative, but the spinal fluid contained 22 cells (60 per cent lymphocytes) and a diagnosis of mild non-paralytic poliomyelitis was made. On discharge July 10, the only positive finding was slight tightness of the neck and back muscles.

Viremia has thus been demonstrated to occur in human as well as experimental poliomyelitis. It has not been found at the time of CNS signs and symptoms, but early in the course of infection, i.e., either during the prodromal period, with the minor illness, or during inapparent infection, presumably a few days after exposure. One of the children whose blood contained virus went on to develop signs of the major illness, mild non-paralytic in type. In recent similar experiments, Bodian and Paffenbarger[38] also have isolated virus from the blood of three children with symptoms of the minor illness. As in the experimental infection, they found that the presence of viremia was associated with a rapid and early rise in specific antibodies.

Turning now to a discussion of the implications of viremia in terms of the pathogenesis of poliomyelitis: The significance of the presence of virus in the blood is not entirely clear. That it occurs regularly in experimental infections seems definite, and it has also been shown to occur in two clinical types of the human disease, as well as in the

asymptomatic human infection. But is viremia an essential feature of the chain of events leading to invasion of the CNS? The answer hinges on the problem of the source of virus in the blood stream, and on this point no conclusive data are available. The following possibilities might be considered: Virus enters through the oropharynx, rapidly makes its way along peripheral nerves to the regional ganglia, where it multiplies, and is "excreted" into the blood, more or less incidentally. In some instances infection stops here; in others, however, the virus continues its neural excursion into the CNS, where further multiplication and spread follow, eventually resulting in the typical clinical picture of paralytic (or non-paralytic) poliomyelitis. This interpretation, a strictly neurotropic one, is held by Faber and his colleagues[39] who have presented considerable evidence drawn from animal experiments to support it. Their experiments in orally infected cynomolgus monkeys have shown that lesions appear in the gasserian, nodose, and superior cervical sympathetic ganglia on the second day after ingestion of virus, and virus multiplication reaches detectable levels on the third day in these ganglia. They conclude that viremia is secondary to multiplication in peripheral ganglia.

In criticism of this interpretation, several points may be raised. First: Although early multiplication of virus in ganglia has been shown, the absence of such multiplication in other tissues, e.g., intestinal mucosa, lymph nodes, spleen, etc., has not been shown. It is entirely possible that active multiplication is in fact going on elsewhere at the same time though no histological alterations are observed. Second: The pattern of involvement of ganglia in orally infected cynomolgus monkeys is not identical with that in human infection. In fact, the findings of Bodian and Howe,[40, 41] using human autopsy material, failed to show a consistent pattern at all which would suggest a definite neural pathway. Third: There is evidence that intact neural connections are not essential for the spread of poliomyelitis virus to the CNS. German and Trask[42] have shown that poliomyelitis can result in animals inoculated cutaneously into a completely denervated limb. Also, inoculation of virus directly into the lumbar cord in animals with complete cord transection at the thoracic level, has produced paralysis *above* the transection in some animals in Howe and Bodian's series.[40, 43]

Another interpretation of the pathogenesis of poliomyelitis involves primary extraneural multiplication of the virus, and assigns viremia a

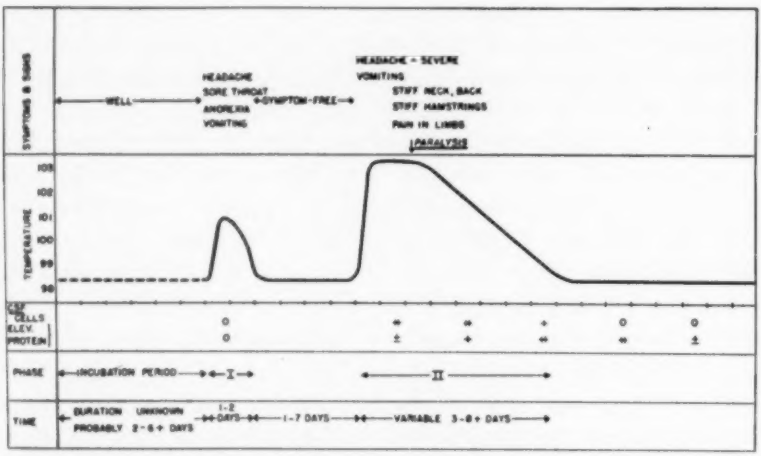

Fig. 11. Diagram illustrating the clinical course of the "childhood type" of poliomyelitis. The first phase corresponds to the "minor illness" syndrome, the second to the "major illness." (From Horstmann, D. M., *Amer. J. Med. 6*:592-605, 1949. Reprinted by permission.)

major role in CNS invasion. According to this interpretation, virus enters the body by way of the oropharynx; the fact that it has been demonstrated in the blood twenty-four hours after ingestion suggests that it may be absorbed directly or by way of lymphatics, and is then distributed to susceptible cells in various peripheral tissues, such as the intestinal mucosa, lymph nodes, spleen, etc., where it multiplies. In a few days, then, it is discharged into the blood where it circulates for several days in considerable quantities, disappearing when antibodies appear. Through the blood it reaches the CNS. According to Bodian,[41] there is thus a primary visceral phase, second, a vascular phase, and thirdly, a neural phase. The experimental evidence to support this hypothesis consists of first, the demonstration that viremia during the incubation period is a regular feature of infection in certain primates after oral and cutaneous introduction of Type 1 and Type 2 virus. Furthermore, viremia has been detected in the human infection, with the minor illness, in the asymptomatic infection, and in the incubation period of the nonparalytic disease. Secondly, Bodian[36] has shown that paralysis after feeding of virus can be prevented in cynomolgus monkeys by passive im-

munization with gamma globulin; he found that small amounts of circulating antibody were sufficient to protect against CNS invasion, presumably by eliminating the viremia. Thirdly, the fact that viremia has always been associated with the *early* appearance of antibodies suggests that the two are related; conceivably the source of virus in the blood is multiplication in those same tissues which produce antibodies; that this is not likely to be nervous tissue is indicated by the observations of Sabin and Olitsky,[44] Morgan,[45] and by von Magnus,[46] that in animals inoculated intracerebrally in which presumably multiplication is occurring only in nervous tissue, antibody production is much delayed.

Relating this interpretation to certain events in the human disease: Figure 11 shows diagrammatically the typical biphasic "childhood" type of clinical poliomyelitis, with a non-specific first phase or "minor illness," and a second phase or "major illness," with neurological signs. The hypothetical course of events might be as follows: a few days after exposure, virus has multiplied in certain peripheral tissues such as the intestinal mucosa, lymph nodes, etc., and can be found in the feces, throat and blood. This period may be asymptomatic, or it may be associated with the non-specific clinical picture of the minor illness. If the infection is to be prevented by means of passive immunization with gamma globulin, the gamma globulin must be given early, before the time of the minor illness and the appearance of viremia. As virus circulates in the blood, it reaches the CNS where it may—or may not—gain a foothold. If it does not, the disease is over; if it does, multiplication and spread may occur, and CNS signs and symptoms develop several days later as the second phase appears. In the meantime, in either case, antibody production has been stimulated, and by the time antibodies reach a detectable level, viremia disappears. This corresponds in time to the onset of the second phase, if it occurs, and the development of CNS signs; if the disease was over with recovery from the minor illness, the patient is now well.

This explanation of the pathogenesis of the human disease is offered as an hypothesis to be proved or disproved. At the present time, no conclusive data are available, and probably not until experiments are carried out which demonstrate the early presence or absence of virus in certain non-neural as well as neural tissues after various routes of inoculation can the problem be solved. Thus, while we have some new ideas—as well as revived old ones—about the pathogenesis of poliomyelitis, the ultimate answers are proving elusive.

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PASSIVE IMMUNIZATION AGAINST POLIOMYELITIS WITH ESPECIAL CONSIDERATION OF THE EFFECTIVENESS OF GAMMA GLOBULIN*

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NO ATTEMPT will be made to recapitulate previously published data,[1-3] but we will try to extend the previous observations. Certain aspects that bear particularly on the practice of passive prophylaxis will be stressed.

It should be recalled that in our studies all injections were given to volunteers, half receiving gamma globulin and half gelatin, by a method of random distribution. Among these children a small number eventually developed poliomyelitis, through normal epidemic exposure. No one, including the members of the research team, knew which type of inoculum any patient had received until after the completion of a 60-day follow-up period and a final muscle examination. Only after a final decision had been reached by all examiners, regarding diagnosis and the presence and degree of paralysis, was the code data regarding type of injection made available. Only paralytic cases are considered in these comparative analyses. All cases that were reported or which could be discovered among either injected or non-injected children of the same age group were examined and followed in an identical manner, by physician and physical therapist members of the team.

We previously described a method of grading the paralytic involvement of patients on a basis of the findings in their sixty day muscle examinations. Grade 1 represented complete recovery from paralysis and Grade 2A recovery to the extent that no muscle was rated below "good" on a scale of "normal," "good," "fair," "poor," "trace," "zero." An additional method of describing paralytic involvement has been added for the final analysis. This we call scoring and represents an

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attempt to classify each patient by the total bulk of effective muscle lost. Each muscle or muscle group tested was assigned a factor based on an estimate of its proportionate bulk. These factors ranged from 0.25 for the smallest muscles to 4 for the quadriceps femoris. This factor was multiplied by a numerical representation of the degree of paralytic involvement, 0 for normal and ranging to 5 for no power or zero strength. Thus, a gastrocnemius, bulk factor of 3 with a "poor" strength rate of 4 would receive a score of 3x4 or 12. The scores of all muscles and groups tested are added to give the patient's score.

Texas

The epidemic in Texas lasted for a number of months, as is characteristic of the poliomyelitis season at this latitude, so the outbreak although reaching a rate of 82 per 100,000 was not exceedingly intense during the period of several weeks immediately following the clinics. Although we feel confident that there was good case finding and reporting among inoculated children, reporting was not as complete among uninoculated persons. Thus, rates in the inoculated and uninoculated populations were not comparable.

Iowa-Nebraska

In the Iowa-Nebraska area an explosive epidemic of record intensity occurred and the period of follow-up netted a very large number of cases for the study. The rate for all cases reported in the area was 427 per 100,000, but this included some over-reporting. Our figures, excluding seventy-eight cases not meeting our criteria for diagnosis gave a rate of 358. Reporting in the urban area was probably equal for injected and non-injected groups but follow-up was less intensive in distant rural areas. Furthermore, the proportion of injected to uninjected children was less in the rural areas. Thus, reporting of uninjected must be considered to be less complete than for the injected. Case rates and the time of peak incidence also differed for urban and rural areas. This would also make a comparison of rates in injection and uninjected children difficult, if not impossible.

Follow-Up

There is little to add to the previous report on incidence in the early weeks, but a small number of cases occurred or were reported and

TABLE I—NUMBER OF CASES OF PARALYTIC POLIOMYELITIS IN STUDY GROUPS, BY WEEK AFTER INJECTION

Week After Injection	*Gamma Globulin*	*Gelatin*	*Total*	*Per Cent Gamma Globulin*
1	12	16	28	42.9
2	3	24	27	
3	3	8	11	
4	1	4	5	15.2
5	0	3	3	
6	3	4	7	
7	3	6	9	35.0
8	1	3	4	
9-13	5	5	10	50.0
Total	31	73	104	29.8

TABLE II—SEVERITY OF CASES OF PARALYTIC POLIOMYELITIS OCCURRING DURING EARLY AND LATER PERIODS AFTER INJECTION OF GAMMA GLOBULIN OR GELATIN, BY GRADE OF 60-DAY MUSCLE EXAMINATION

Severity of Case	*Period After Injection*					
	1 week			*2-8 weeks*		
	G.G.	*Gel.*	*%G.G.*	*G.G.*	*Gel.*	*%G.G.*
All paralytic cases	12	16	42.9	14	52	21.2
Paralytic excluding Grade 1	6	15	28.6	12	44	21.4
Paralytic excluding Grades 1 & 2A	0	5	0.0	9	30	23.1

followed subsequent to the time selected for the preliminary report. Final results are shown in Table I. No significant reduction in the number of cases was observed during the first week after injection. The greatest reduction occurred from the beginning of the second week through the fifth week. Protection appeared to dwindle following the fifth week and from the ninth through the fourteenth week an exactly equal number of cases occurred in those receiving gamma globulin and in the control group given gelatin.

Modification of the disease among those injected within seven days of the onset of illness was suggested by data previously presented.[3]

TABLE III—SEVERITY OF CASES OF PARALYTIC POLIOMYELITIS OCCURRING DURING FIRST WEEK AFTER INJECTION OF GAMMA GLOBULIN OR GELATIN, BY SCORE OF 60-DAY MUSCLE EXAMINATION

Inoculum	*Muscle Involvement Score* 0	1-9	10-19	20-29	30-39	40-59	60-79	80-99	100+	*Total*
Gamma Globulin	6	3	2	1	0	0	0	0	0	12
Gelatin	1	7	4	2	0	0	1	1	0	16

TABLE IV—MODIFICATION OF PARALYSIS DURING FIRST WEEK AFTER INJECTION

		Gamma Globulin	*Gelatin*
Muscle Score	> 7.25	3	11
	< 7.25	9	5

Modification has been amply confirmed by further analysis. It was reported previously that six of the twelve cases in the gamma globulin group recovered completely. Only one of the sixteen in the gelatin group fared equally well. These differences are significant. In Table II it may be observed that by eliminating cases of Grades 1 and 2A, most of which would not have been reported as paralytic cases had any but a research type of follow-up been instituted, the results would be described as protection, rather than modification. In Table III, a comparison of scores for the gamma globulin and gelatin groups is presented. Here again the differences in severity are obvious. Table IV, a four-fold table of severity ratings above and below a score of 7.25 shows a very significant difference. This difference would be expected to occur by chance less frequently than two times in a hundred. Mean and median muscle scores further support the modification of disease by gamma globulin during the first week after injection.

After this first week, those cases which occurred in the gamma globulin group appear to have been as severe as those occurring in the group given gelatin (Tables II and V). Mean muscle scores also support the assumption that no modification of disease occurred.

From the data just presented, and assuming the usual incubation

TABLE V—SEVERITY OF CASES OF PARALYTIC POLIOMYELITIS AMONG INJECTED AND NON-INJECTED CHILDREN OF SIMILAR AGES, BY SCORE OF 60-DAY MUSCLE EXAMINATION

Inoculum	*Muscle Involvement Score* 0	1-19	20-39	40-99	100-199	200-399	400+	*Fatal Cases*	*Total*
Gamma globulin*	1	9	2	2	2	1	1	1	19
		63.2%				36.8%			
Gelatin	8	26	16	13	5	2	2	1	73
		68.5%				31.5%			
Not injected	11	29	14	25	20	17	1	4	121
		44.6%				55.4%			

* Cases occurring during first week after injection have been omitted.

TABLE VI—COMPARATIVE DISTRIBUTION OF HIP PARALYSIS IN CHILDREN WITH RESIDUAL PARALYSIS AT 60-DAY EXAMINATION IN GELATIN INJECTED AND NOT INJECTED GROUPS OF SIMILAR AGES

Paralysis	*Gelatin Injected** *No.*	*%*	*Not Injected†* *No.*	*%*
Rt. Hip	26	57.8	56	61.5
Not Rt. Hip	19	42.2	35	38.5
Total	45	100.0	91	100.0

* During the first 4 weeks after actual day of injection.
† During the week of opening clinics plus the next 4 weeks.

period of poliomyelitis to be seven to fifteen days, we conclude that when gamma globulin is given following infection, it may be expected to prevent or modify the clinical manifestations in most instances, such as occur in measles. When gamma globulin is given before infection it usually prevents the paralytic disease, but, when it fails, there is no evidence that the disease is modified.

VALIDITY OF GELATIN CONTROL GROUP

Since conclusions of the study have been based on a comparison of rates between a control group injected with gelatin and a group given gamma globulin, we must examine the possibility that an inoculation of gelatin may have increased the incidence of paralytic disease. Since certain immunizing injections and some of other types have been reported

TABLE VII—PARALYTIC CASES,* CASE RATES BY AREAS AND TOTAL ADJUSTED RATES, BY INJECTED AND NOT INJECTED GROUPS

Area	*Injected*				*Not Injected*			
	Gamma Globulin		*Gelatin*					
	Cases	*Rates*	*Cases*	*Rates*	*Cases*	*Rates*	*Exp.†* *Cases*	*Adj.* *Rate*
Utah	1	.350	5	1.748	12	1.765	5.05	
Texas	10	.604	19	1.147	76	.840	13.92	
Iowa	14	1.765	42	5.294	39	5.303	42.07	
Total	25	.914	66	2.412	127	.....	61.04	2.23

* Cases occurring during the period of 14 weeks after closing clinics.

† Expected number of cases calculated by applying rate to standard population which was that of the gamma globulin or gelatin groups.

to have provoked paralysis, our data have been examined for this possibility.

Most conspicuous in other studies has been a localization of paralysis in the injected limb. Table VI presents one of several analyses prepared for the cases occurring within four weeks after injection. All injections were given in the right buttock. None of the analyses, whether for the hip or the leg, or for both hips or both legs or any other pattern of possible localization has suggested any localizing phenomenon for the gelatin inoculated group.

In comparing rates, it must be recalled that under-reporting among the uninoculated, particularly in Texas, would give a false impression of increased incidence in the injected. The data in Table V support our belief that there was under-reporting of mild cases in the uninjected. If we assume that there was equal reporting of patients with muscle scores over 200 and of fatal cases, an estimate of 58 per cent under-reporting is obtained. There are also other obvious reasons, which we described previously,[1] why the two groups would not be comparable. Therefore, any differences must be large if they are to have any significance. A variety of analyses has been made and no differences considered significant have been found. In Table VII it will be noted that rates in the uninjected and in the gelatin injected groups were essentially the same in each area except Texas, where under-reporting of the uninjected was known to be large. The adjusted total rate for all areas combined is 2.23 per 1,000 for the non-injected and 2.41 for those injected with gelatin. This slight difference has no significance. If correction is made for

under-reporting in the uninjected the difference is then in the opposite direction.

For a moment, let us disregard the gelatin controls, however, and consider the gamma globulin and non-inoculated groups. In every area, except Texas, the differences are statistically significant, and even in Texas the gamma globulin inoculated group has a lower rate. The total adjusted rate for the uninoculated for all areas (2.23) is much higher than that of the combined groups receiving gamma globulin (.914). This is very significant ($X^2=14.8$; $p<.001$). Thus, if we are interested only in the question, does or does not gamma gobulin protect, the answer appears quite clear even without gelatin injected controls. This would not have been possible had gamma globulin been less effective, had fewer children been inoculated or had the selected epidemics been less severe and the timing less satisfactory.

Use of Gamma Globulin

It is unfortunate that so much dependence and hope for a prophylactic agent must be focused on gamma globulin at the moment. It merits this hope and attention only because it alone has been shown to be a safe agent capable of preventing paralytic poliomyelitis. It is effective, however, only under distinctly limited circumstances. If these limiting circumstances were understood there might be less enthusiasm about it and possibly less demand for it. However, until something better becomes available, every possible effort must be made to meet a reasonable demand and to use available amounts intelligently.

Let us consider the contrast between certain pertinent characteristics of poliomyelitis and measles. In measles, infection is almost invariably associated with clinical disease of a fairly severe nature. The time of exposure is frequently recognized and susceptible children needing protection can usually be selected from the immunes by asking a simple question—"Has this child had measles?" Since the time of infection is presumably known when an injection of gamma globulin is made, only 1 or 2 cc. are needed, to give protection for a very brief period of time. In such a disease, passive prophylaxis, in the absence of active artificial immunization, has proved to be of real benefit. Some benefit probably occurs from at least 50 per cent of all injections given. In other words, for every two children injected, at least one derives benefit by prevention or modification. Poliomyelitis, however, does not resemble

measles in any of these respects. Most poliomyelitis infections are not associated with clinically recognizable disease; exposure is rarely suspected at the time it occurs and susceptibles needing immunization cannot be readily identified. As a result, hundreds or thousands of injections must be given to provide protection—essentially by accident—to one or two who actually need it and may profit. Furthermore, the dose given must be large, for since the time of exposure is usually unknown, if exposure occurs, the period of protection must be extended; 0.14 cc. per pound of body weight protects for about five weeks.

Some of the circumstances under which gamma globulin might be used are as follows:

1. *Mass Prophylaxis:* The controlled tests were carried out as mass prophylaxis in an epidemic community because this appeared to be the most effective way to conduct an experiment to obtain the desired information. This was not done to establish a pattern for the future use of gamma globulin. However, there appear to be circumstances under which more or less simultaneous injection of all children of the most susceptible age, for that particular community, would prevent the greatest number of cases per thousand injections given. Such communities would be those of north temperate latitude where the total duration of the outbreak may be expected to be fairly brief; where a reliable epidemic forecast can be made well before the peak and where the total rate for the season can be expected to attain (and actually does attain) a figure of 150 per 100,000 or more. In our experience, the Iowa-Nebraska outbreak was the most ideal, with one case prevented for each 250 to 300 injections given. In Houston and Harris County, Texas, lower rates and a more prolonged epidemic pattern combined to lower the effectiveness to one case prevented for every 2,000 injections given. With quantities of gamma globulin limited, use in the latter type of outbreak is unreasonable. This means that gamma globulin used for indiscriminate mass prophylaxis would not be particularly effective in cities of over 150,000 population where rates above 100 per 100,000 are very rarely encountered, nor in the extreme south of our country where the epidemic season is usually extended.

2. *Family Contacts of Diagnosed Cases:* Use in family contacts of diagnosed cases approaches the pattern employed in measles, but, as pointed out above, great differences exist. It is only natural that physicians who hoped gamma globulin might prevent poliomyelitis have used

it in this way for a number of years. There is still no direct evidence that gamma globulin will be effective when so used, but much indirect and epidemiologic evidence supports the belief that except in areas of severe epidemic conditions, more cases will be modified or prevented by this method than when employed as an indiscriminate, mass procedure. Nevertheless, the sharp limitations in its effectiveness must be appreciated. Only about 5 per cent of polio cases give rise to a second case in the family, so at least 95 per cent of the globulin so given would be wasted and not more than 5 per cent of the subsequent cases in the community could be prevented by this use. The effectiveness, however, is still further limited. In a large series of family studies from epidemic and non-epidemic areas, made by various workers, including ourselves, it appears that approximately 60 per cent of all secondary cases have occurred by the fifth day after onset of the index case. Likewise, we observe that the average time between onset and diagnosis is four to five days. Thus, this 50 to 60 per cent of all secondary cases will have become ill before the physician is in a position to inject the other members of the family. If injections are performed at this time (fifth day), on the basis of our data for cases occurring within seven days after injection, modification of severity (with few completely protected) would be anticipated among those who would be expected to develop the disease during the next week (five to twelve days after onset of index case). Approximately 30 per cent of all secondary cases normally occur during this period. After this time only 10 per cent of all secondary cases are expected. Most of these should be prevented by gamma globulin. Actual family rates have been computed for this last 10 per cent of cases occurring more than twelve days after the onset of the index case, but numbers are small and standard deviations large. It appears, however, that these rates (for *all ages* in the family) are higher than those for *all children* under fifteen years of age in the community, except where epidemic rates attain levels of 300 to 500 per 100,000 or greater for the total epidemic. In families, there is a tendency for the later secondary cases to occur among the older children or adults, thus it would appear wise to extend the age coverage in families to include younger parents and certainly all pregnant women.

The distribution of second cases in family groups, for poliomyelitis and measles, is shown in Chart 1 by day of onset after initial case. The possible reason for the difference in the shape of the curve for per cent

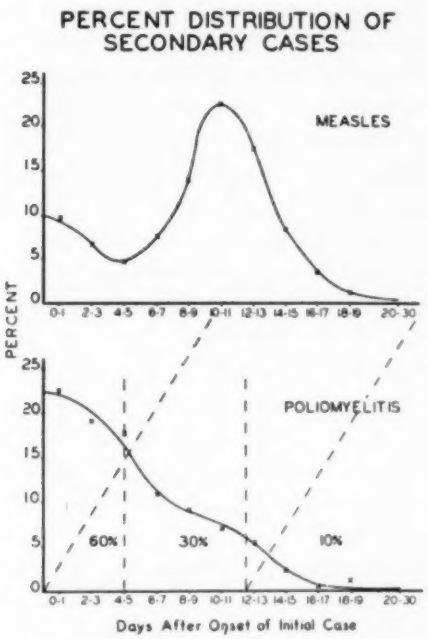

CHART 1.—Data on measles from "Measles and Scarlet Fever in Providence, R. I., 1929-1934 with Respect to Age and Size of Family" by Edwin B. Wilson, Constance Bennett, Margaret Allen and Jane Worcester. *Proceedings of the American Philosophical Society, 80:* No. 3, February, 1939.

distribution of secondary measles and poliomyelitis cases is believed to be due to failure to recognize the primary poliomyelitis infection in the family, since it is much more likely to be an abortive or inapparent type than one that can be clinically diagnosed. This would appear reasonable since only 1 of 100 or more infections with poliomyelitis virus appears to be clinically recognized. This undiagnosed, primary infection then leads to multiple secondary infections, among which may occur one with clinical manifestations permitting diagnosis. This would be the index case leading to the family. This point in family experience (undiagnosed primary infection) is thus comparable to the primary case in measles which leads to the wave of secondary measles cases. The peak

is sharper in measles and the fall off more rapid because of an incubation period of a much more constant length.

3. *Intimate Contacts, other than those of the Family:* There are no statistical studies of a scale and nature similar to those for family contacts, so little can be said for such application. For administrative purposes, these contacts are difficult to define, yet certain extrafamilial contacts would appear to have exposure equal to that of family members.

4. *Familial Contacts of Suspect Cases:* The more severe a poliomyelitis epidemic becomes, the higher will be the proportion of undiagnosed febrile illnesses that are actually abortive poliomyelitis. A certain number of these will probably represent primary family infections. Under severe epidemic conditions, if gamma globulin were given to family contacts of suspect cases the possibility of injecting children in a number of families at the time one does in measles (soon after exposure to the primary infection) might well more than compensate for its use in families where the suspect case was not actually abortive poliomyelitis. No certain advantages over mass prophylaxis could accrue from use in contacts of suspect cases except under the occasional epidemic condition just described and in families in which the suspect case was subsequently diagnosed as poliomyelitis, and in which the siblings were injected a few days earlier because action was taken at the time diagnosis was suspected, rather than confirmed. However, when compared to simultaneous, indiscriminate mass immunization of all children of certain ages in a community with an equally severe epidemic, this "suspect case-contact" method would appear to be at least as selective and effective, if not more so. It could be considered as a compromise method, used to include more children in the immunization program than only contacts of confirmed cases, but fewer than *all*. While gamma globulin is not available for *all*, this might serve as one method for limited distribution, providing attack rates are high enough to justify *any* type of program beyond the most limited type.

5. *Treatment:* There is absolutely no evidence that injection of any quantity of gamma globulin will affect the course of disease once illness has begun. In fact, the work done by Bahlke and Perkins[4] in New York State years ago demonstrated that very large quantities given during the pre-paralytic stage were without any effect. Therefore, we must insist that this scarce material be not wasted in large amounts in a manner in which there is evidence that it is not effective.

I much prefer to have undertaken the review of the limited usefulness and effectiveness of gamma globulin before others who might infer that I was too far sighted to see the imperfections of a progeny I had helped to sire. Now, however, I feel impelled to say *something* in favor of the gamma globulin project. After all, I did promote this project for a considerable period of time before it became a reality, then supervised it; and I still feel justified in having done so.

First, because I believe this has offered another example of how a new immunizing agent can be tested and how a definite answer to its effectiveness can be obtained in minimal time.

Next, when this plan to test the effectiveness of gamma globulin in man was conceived and until it was actually undertaken in Utah in September 1951, there was no animal experimental work to indicate that protection was afforded against the paralytic disease by anything short of very high levels of serum antibody. These levels could be attained in animals only by repeated vaccination with large amounts of virus-containing tissue, or large amounts with an adjuvant, or by injecting massive amounts of gamma globulin, represented by several liters when translated to the size of a child. Neither passive nor active immunization appeared easy to attain. It was my impression—not knowledge—from simple reasoning, that artificial laboratory experimental procedures in animals did not duplicate natural exposure of the natural human host and until immunization in man had been tested, no conclusions should be drawn. Most scientists and fellow workers wished me well in the project but gave little encouragement regarding the outcome—in fact, doubted that low titers of antibody would protect. I obviously believed it might, but was spurred on largely by curiosity and by the importance of the knowledge, regardless of the outcome. For, if gamma globulin in the limited dose employed could give protection, such levels of antibody could be readily attained subsequently even by a comparatively poor antigen preparation. Calculations indicated that the amount of antibody we proposed to inject could probably not even be detected or be detected only in an equivocal manner by current methods of testing.

The effectiveness of antibody at this level has now been demonstrated, with the aid of many colleagues in an extremely costly and difficult type of project. However, consider the difficulties that would face the investigator with an *active immunizing agent*, who attempted to gather the *same* information. The number of cases in the vaccinated

and controls would have to approach the same limits we set for significance, but since immunization would have to precede the date of exposure by at least several weeks, and since injection of an immunizing antigen, particularly a depot antigen, would be feared during an epidemic because of danger of provoking poliomyelitis, all study areas would have to be selected and the injections performed one or more months before the occurrence of an epidemic. Imagine the cost and effort of such an undertaking carried out in a manner that would obtain significant results.

It is my firm belief that such an undertaking is no longer necessary, since it has been demonstrated with passive protection that a low level of antibody affords protection. A vaccine which consistently produces at least such a level in a relatively small number of children and will maintain this critical level for the desired period of time should be accepted as effective. It would remain only to prove that it was safe! This alone is no small undertaking! This demonstration of the low, effective level of antibody, I believe to have been the real importance of the gamma globulin tests. Now, I wish it were possible to spare the physicians, the administrators, the public and myself from this intermediate period when gamma globulin must be *used* since it is the only means of protection. I recognize that it has produced many difficult problems. I hope that better days are ahead, when a vaccine will replace it to a very large extent.

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ACTIVE IMMUNIZATION AGAINST POLIOMYELITIS*

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MR. PRESIDENT, Fellows and guests of the Academy, Dr. Hammon has just told you of some of the beneficial aspects as well as some of the drawbacks of gamma globulin (immune serum globulin) therapy, and I am sure that we most certainly agree with Dr. Hammon that immune serum globulin is not the final answer to the problem of long-term protection against poliomyelitis. The various shortcomings of immune serum globulin therapy have been discussed in considerable detail elsewhere,[1] so that it is not necessary to discuss that phase of the problem at this time. Without doubt, the only approach to the poliomyelitis problem is to bend every effort to develop a safe and practical immunizing agent: a vaccine that will give long-lasting protection against the disease. To that end, we have the possibility of developing either a killed preparation or a living attenuated virus vaccine.

Other investigators such as Morgan[2] have shown that monkeys inoculated repeatedly (12 to 15 times) with inactivated poliomyelitis virus–infected spinal cord tissue of monkeys treated with formalin–produce neutralizing antibody in fairly high titer and show measurable resistance to challenge with virulent virus. Recently, Howe[3] has reported some preliminary trials carried out in man with inactivated vaccines prepared from spinal cords of infected monkeys. Killed vaccines of this type, prepared from infected central nervous tissue, may be dismissed immediately from practical consideration, first, because poliomyelitis virus cannot be concentrated and readily freed of the nervous tissue components which are responsible for producing allergic encephalitis; and second, it is doubtful that enough monkeys are available to produce such a vaccine in the necessary quantities. I might add that the two primary factors that caused us[4-10] to develop the living avianized rabies vaccine

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were: One, we were not able to develop a satisfactory method of freeing brain tissue vaccines of the factor or factors responsible for producing allergic encephalitis and still retain a stable and potent product; and two, we wished to provide longer lasting protection than that usually afforded by killed vaccine. Common sense dictates that we should profit somewhat at least from the sad experiences we have had with rabies vaccines prepared from nervous tissues and not risk inducing the same paralytic accidents with a vaccine for poliomyelitis.

Recent advances in the field bear great promise that in the foreseeable future a method will be developed whereby we can produce a satisfactory vaccine for protection against poliomyelitis. One of these developments is the work of Enders and his associates[11-19] who first showed that it is possible to grow all three types of poliomyelitis virus in cultures of non-neural tissues of human origin. This procedure, of course, obviates the risk of causing allergic encephalitis since non-nervous tissues such as kidney, uterus or muscle are used. This approach for solving various aspects of the poliomyelitis problem, such as virus detection, propagation, assay, antibody quantitation, preparation of diagnostic antigens and of vaccines has been pursued by numerous workers in the field, including Salk and his associates at the University of Pittsburgh,[20-22] Melnick at Yale,[23-27] Syverton at the University of Minnesota,[28-32] Rhodes at the University of Toronto[33-35] and Evans at the University of Washington.[36, 37]

At this time I wish to point out that any vaccine prepared from tissue cultures which contain mammalian cells taken at surgery or from sacrificed animals must of necessity be a killed vaccine. Because of the inherent danger of picking up extraneous contaminant viral, rickettsial, bacterial or carcinogenic agents, it would be unwise and impractical for anyone charged with the responsibility of commercial vaccine production to assume the risk of producing a living, modified virus vaccine from explanted tissues derived from a mammalian source.

Recently, Salk[38] reported preliminary experiments wherein he vaccinated approximately 161 human volunteers with formalin-killed virus vaccines prepared from tissue culture materials using either minced monkey kidney or monkey testicle. He found that if given intradermally as an aqueous preparation the vaccine induced an antibody response only against the Lansing, Type 2 virus. A water-in-mineral oil emulsion type of killed vaccine prepared from all three types of poliomyelitis virus

(Brunhilde, Lansing and Leon) was claimed to induce antibody response against all three types when the vaccine was administered intramuscularly. The antibody levels of the vaccinated subjects were determined by tissue culture technique.

It should be noted, however, that all antibody titers reported were on sera taken a very short time after vaccination, i.e., not longer than four to seven weeks post-vaccination. Furthermore, significant antibody levels were found in most of the people *prior* to vaccination; namely, in six of twelve against Type 2, seven of sixteen against Type 3 and all fifteen out of fifteen against Type 1 poliomyelitis virus. It must be realized, of course, that it is much easier to demonstrate the antigenic booster effect or anamnestic response to an antigen by vaccinating individuals who have had a previous experience (immunizing infection) with the antigen than it is to stimulate antibody production in persons who have never had any previous exposure to the agent. Thus critically reviewed. Salk's results are not too impressive.

Salk also indicated that mineral oil adjuvant was necessary to make the tissue culture virus antigens become immunogenic, and that vegetable oils could not be used as a substitute for mineral oils.[39] It is difficult at the moment to evaluate fully Salk's results, for many of his experiments were not completed when his report was published. However, I believe it is not out of order to utter a word of caution about certain potential complications that may arise from such a vaccine preparation. While animal experiments have failed to demonstrate any carcinogenic action of certain highly refined paraffinic mineral oils,[40] especially Russian or Pennsylvania oils, which are essentially free of aromatic compounds,[41] there is always the possibility that malignant tumors might occur in particularly susceptible individuals. Furthermore, it should be remembered that mineral oils are not saponifiable and that they behave essentially as a foreign body in the tissues of the host. They are not hydrolyzed but remain unchanged and physiologically inert for long periods of time, probably for life, regardless of how administered. The reactions to such oils have been described as foreign body granulomata, benign oil tumors, oleomas or oil cysts, which sometimes result in slow-healing abscesses.[42, 43]

It should be noted that the surest way apparently to determine carcinogenicity of an oil is to inject it into a large number of mice, rats and rabbits *intramuscularly*, once a month for at least three months, and

observe the animals for the *rest of their natural lives*. In extensive experiments by this procedure, Hueper[44] has demonstrated sarcoma formation with oils that were entirely non-carcinogenic when applied to the skin. It is evident that it would be most difficult, if not impossible, for a commercial biological laboratory to carry out such tests on each and every lot, or production batch, of oil used for vaccine preparation. Yet no one can deny the fact that such tests should be carried out if the product is to be considered safe.

In any case the oils remain in the tissues for years, and in individuals who give an extensive foreign body response, surgical removal of the tumors may be required. It is possible that killed vaccines which contain mineral oil as an adjuvant will give stronger and longer lasting immunity than killed vaccines in an aqueous base, yet it is most doubtful that either will give as long-lasting immunity as will a living, attenuated virus vaccine.

It probably will be necessary to revaccinate with the killed vaccines every two to three years in order to maintain the desired state of protection. When one considers that the product will be used primarily in young children and that the mineral oil component of each injection may persist in the tissues for life, it at once emphasizes the need to proceed with caution. Any procedure which requires repeated vaccinations over the years greatly increases the chances of sensitizing the individual to foreign proteins injected and cannot be considered as the ideal solution to the problem at hand.

In other words, the mineral-oil-adjuvant vaccine approach *may be* a safe procedure, but that can be proved only over a long period of time and should be determined only with a limited number of vaccinated persons. Certainly it will take much more time to evaluate the safety of a mineral-oil-adjuvant type vaccine than it will a living, attenuated virus vaccine. It would prove to be most embarrassing to have a situation develop comparable to that encountered with killed rabies brain tissue vaccines wherein the vaccination procedure actually causes a greater number of deaths or unfortunate sequelae than occur among the unvaccinated who have been exposed similarly.[45, 46]

Another approach towards solving the problem is to secure in tissue culture a pure line strain of normal mammalian cells, either human or animal in origin, proven to be free of any extraneous viral or bacterial contaminants and known to possess no carcinogenic activity. If it were

possible to maintain such a pure line strain of normal cells in tissue culture and to propagate the cells in large enough quantities to meet our research and production needs, we would have a very useful medium. Unfortunately, at the moment we do not have the necessary information to accomplish this task, but the problem is worthy of a great deal of attention and energy.

By using a stable strain of human malignant epithelial cells (Héla strain), derived from an epidermoid carcinoma of the cervix, for the cultivation of all three types of poliomyelitis viruses, Syverton and his associates[32,47] have been able to quantitate antibodies by the neutralization technique, to produce virus in quantity in serial passage and to isolate and type viruses rapidly. This is a significant contribution but it is indeed unfortunate that the Héla strain is of neoplastic origin. Of course, it would be the medical discovery of the century if it were found that a chemically inactivated poliomyelitis vaccine prepared from tissue culture cells of the Héla type was carcinogenic, but that potential danger must be considered. Thus, at the moment at least it is most doubtful that anyone would recommend the use of neoplastic cells in tissue culture as the medium for producing poliomyelitis vaccine.

Before proceeding, I wish to emphasize that the tissue culture technique is an extremely important tool, especially for research purposes, where it can be applied to so many problems such as isolation, identification and propagation of infectious agents, quantitation of antibodies and assay of infectious agents by the neutralization technique, and for the development of virus mutants or variants which may be adapted to new and ordinarily non-susceptible hosts. I might add that we are interested particularly in this latter application of the technique because it has unlimited possibilities. Just recently, Li and Schaeffer reported[48] an important application of this procedure to establish the Brunhilde strain of poliomyelitis virus in albino mice.

I believe it is appropriate to note at this point that tissue culture methods have been recognized and previously used to good advantage to solve other difficult problems. The highly dramatized problem of poliomyelitis is not the first instance in which tissue culture procedures have been applied successfully in order to get a "foot in the door." As a matter of fact, both Theiler[49-51] and I[52-58] used tissue culture procedures as research tools or intermediate steps in the development of the 17D living virus, yellow fever vaccine and the killed rickettsial vaccines

against Rocky Mountain spotted fever, epidemic typhus fever and Q fever that are being produced commercially today.

Theiler and Smith[49,50] used cultures consisting of minced chick embryo containing minimal amounts of nervous tissue to procure the 17D variant of the Asibi strain of yellow fever, which is used today as living, attenuated virus vaccine. A similar mutant strain of yellow fever apparently was obtained subsequently by Penna and Moussatché.[59] I used cultures consisting of various tissues of the developing embryonic chick to determine that the yolk sac is quite superior to other tissues for growing all types of rickettsiae in large quantities.[52,54,55,58] This observation led to the yolk sac method of inoculation of fertile hen's eggs which is used today for the propagation of practically all viral and rickettsial agents.[60]

The tissue culture method was shown previously to be more sensitive than animal inoculation for detection of minimal quantities of at least one other neurotropic virus. Thus, in 1936 I[61] reported that the inoculation of tissue culture preparations was a considerably more sensitive method for detection of minimal quantities of Eastern equine encephalomyelitis virus than was the usual procedure of inoculating guinea pigs or mice intracerebrally. So far as I know, the only vaccines being produced on a comparatively large scale by tissue culture methods are those against foot-and-mouth disease, developed by Frenkel,[62-66] and hog cholera, developed by Boynton.[67,68*] It should be noted that both these vaccines are used only in the field of veterinary medicine and that one is a killed vaccine (foot-and-mouth disease), while the other is a living virus preparation that is used in conjunction with immune serum (hog cholera).

Still another approach towards solving the poliomyelitis problem is to develop a living modified virus vaccine. Without doubt the most practical and greatest success in immunizing man and animals against viral infections has been achieved thus far with the use of living modified or attenuated viruses. In the case of human infections I point out specifically

* By the standards of a tissue culture specialist his method is comparatively crude, but Frenkel has introduced some very ingenious, time and labor saving devices which give a practical tissue culture medium for producing foot-and-mouth vaccine against at least three immunologically distinct types of the virus (European A, O and C types), using explanted epithelial tissue of the bovine rumen or tongue. Frenkel's problem has been somewhat simplified in that maximal growth of the virus (titers of 10^{-6} or greater) is obtained within eighteen to twenty-four hours. This, of course, greatly facilitates the suppression of bacterial contaminants by using antibiotics or sulfonamides. Frenkel's final product is a formalin-killed vaccine. Boynton used swine bone marrow or other swine tissue explants suspended in suitable physiological media. The hog cholera virus was presumably attenuated for swine by prolonged passage in tissue culture and is now produced commercially. The product recommended for field use consists of simultaneous injections of living virus propagated in tissue culture and immune serum, thus indicating that the cultured virus may be partially but not completely modified in its virulence for swine.

smallpox, yellow fever and rabies; in the case of veterinary medicine I mention rinderpest, South African horse sickness, blue tongue of sheep, fowl pox, pigeon pox, infectious laryngotracheitis of chickens and the new products which recently have been developed and produced in my laboratory, such as "wing web" vaccine and "intranasal" or "conjunctival" vaccine for Newcastle disease,[69-72] chick embryo propagated distemper vaccine,[73-78] chick embryo propagated rabies vaccine[4-10] and the rabbit adapted hog cholera vaccine.[79-82]

Returning to the problem at hand, namely, poliomyelitis, a review of the literature indicates that the two most promising paths for inducing immunity are the intramuscular and oral routes. Further, evidence obtained in the use of other living virus vaccines strongly indicates the importance of using the natural portal of entry whenever possible to achieve maximal beneficial effects of the immunizing agent.

We now recognize that large epidemics of paralytic poliomyelitis in certain countries are apparently a reflecton of improvement in sanitary conditions. By improving our living habits we have altered or upset Nature's balance so that instead of having a symbiotic relationship between the host and the infectious agent we have actually created a non-immune population wherein large epidemics of paralytic poliomyelitis can be expected and do occur. In those parts of the world that have not improved their living and sanitary habits poliomyelitis epidemics are apparently rare and relatively unimportant, and paralysis when it does occur is almost always limited to children of the younger age groups. As the virus is very widely distributed in these so-called "under-privileged" areas, most people come in contact with it while they are quite young and progressively acquire their immunity in all probability through infection by way of the oral and gastrointestinal routes so that paralytic poliomyelitis in these countries is comparatively rare.[83] I am of the opinion that probably the most logical and practical way to immunize infants and children against poliomyelitis is to follow the pattern that seems to take place so universally under natural conditions; that is, to use an attenuated, living virus under biologically and quantitatively controlled conditions by a natural portal of entry—the oral route.

I believe that the studies carried out in our laboratory with the "intranasal" or "conjunctival" type of Newcastle disease vaccine have served as a very useful model for much of our poliomyelitis work. Thus, my colleagues Doctors Markham and Bottorff[71,72] have demonstrated

that by using the proper quantitative conditions a single drop of the relatively avirulent Blacksburg strain of Newcastle disease virus will readily immunize either fully susceptible, or passively immune, one-day-old baby chicks, provided the portals of entry of natural virus infection, namely, the intranasal or conjunctival routes, are used. Such vaccinated birds show no signs of illness following vaccination and often fail to develop any appreciable antihemagglutinins, particularly if the virus menstruum possesses no unusual surface activity; yet they will readily withstand intranasal challenge of at least a million lethal doses of highly virulent field strains of virus seven to ten days and five, seven and ten weeks later. Surface active agents, which possess no anti-viral activity, greatly enhance the serological response induced by intranasal vaccination. In contrast, a negative or irregular immune response is obtained when the same or much greater quantity of the Blacksburg strain of virus is administered to passively immune birds via unnatural portals of entry such as the intraperitoneal, subcutaneous or intramuscular routes. The receptor cells of the respiratory tract, the natural portal of entry, are free to receive the virus introduced regardless of the state of passive immunity of the host. The virus becomes established and multiplies sufficiently to create a local barrier of actively immune cells at the portal of entry. A period of seven to ten days is required for birds to become immune by using the Blacksburg strain of virus under these conditions. During this period the birds should be kept in clean quarters, free from virulent strains of Newcastle disease virus, because no appreciable cell-block or interference effect is produced by the Blacksburg strain of virus when used in this manner. This strain is of such low virulence, or spreading-potential, that contact infection is ordinarily not transmitted from vaccinated to fully susceptible, unvaccinated chicks housed in the same brooder. After the immune state has become established, the vaccinated birds are able to withstand tremendous doses of extremely virulent viral suspensions introduced either intranasally or in the conjunctivae. To date, more than 460 million birds have been vaccinated with this product. The birds, in spite of their systemic immunity, obviously sustain at least a localized, clinically inapparent infection following challenge because they show very marked rises in antibody levels. This mechanism of inducing initial, basic immunity followed by "booster" challenges of living virus via a natural portal of entry seems to be paralleled in Nature by infection with poliomyelitis virus. To

achieve successful immunization against poliomyelitis the goal is to duplicate the processes of natural infection under biologically and quantitatively controlled conditions.

As early as 1934, Kolmer and Rule[84] fed living poliomyelitis virus to rhesus monkeys in an attempt to immunize them. Unfortunately, an immune response was not engendered because the wrong experimental host was selected for these early studies. Recently, Koprowski, Jervis and Norton[85] carried the work a step further by feeding human volunteers a living rodent-adapted poliomyelitis virus. Briefly, the virus consisted of a suspension of brain and spinal cord tissues of cotton rats infected with the TN strain, Lansing type, poliomyelitis virus. A total of 20 children were fed dosages ranging from 1 ml. to 10 ml. each of the cotton rat tissue suspensions. All individuals were observed carefully but none showed any signs of illness nor were any temperature rises noted. Most of the subjects became intestinal carriers for a short time of the virus strain that was fed. All subjects that were not initially immune developed neutralizing antibodies to the homologous Lansing type virus, but not to the heterologous Brunhilde type virus. Further work carried out by my laboratory in conjunction with the California State Department of Public Health, the California State Department of Mental Hygiene and the George Williams Hooper Foundation of the University of California has confirmed and somewhat amplified the above studies.[86]

While I subscribe fully to the thesis that the use of living, attenuated virus offers the most logical and hopeful approach towards solving the poliomyelitis problem, I am of the opinion that the virus should not be propagated in infected mammals nor in infected mammalian explanted tissues until other approaches have been exhausted. Those responsible for producing vaccines commercially recognize that such infected mammalian tissues are not ideal to use because they always present the danger of being contaminated with other viruses or microbic agents that are infectious for man. These include lymphocytic choriomeningitis, infectious hepatitis, Sabin's B virus, encephalomyocarditis viruses, et cetera.

I believe that the poliomyelitis problem would be greatly simplified if the developing chick embryo could be used as the propagating medium since it has proved to be so nearly the ideal host for mass-producing many other living attenuated viral vaccines, such as yellow fever, smallpox, rabies, blue tongue of sheep, rinderpest, Rift Valley fever, Newcastle disease, canine distemper, fowl pox, pigeon pox and infectious

laryngotracheitis of fowls; and killed viral and rickettsial vaccines, such as Rocky Mountain spotted fever, epidemic and murine typhus fever, Q fever, influenza, mumps, Western, Eastern and Venezuelan equine encephalomyelitis and Japanese B encephalitis.[60] The chick embryo possesses the admirable qualities of always being readily available, easily handled, relatively cheap and above all free from microorganisms potentially dangerous for man. Furthermore, the chick embryo has a marked advantage in that it is not a natural host for poliomyelitis virus and if a mutant strain can be established there is very little likelihood it will regain its virulence for man.

Until quite recently poliomyelitis virus was one of the comparatively few viruses that had resisted cultivation in developing chick embryos. However, during the past year workers in my laboratory have demonstrated that at least one strain of poliomyelitis virus can be cultivated in this host.[1, 87, 88] This work was started four to five years ago by Dr. Moyer and myself[89] in an attempt to develop a more practical method for producing complement-fixation diagnostic antigens. By carrying each of two sub-lines of the virus (A and B series) through more than 150 serial transfers in suckling hamsters, using the intracerebral route of inoculation and infected brain tissue for passage, Moyer[89] brought about a modification of the MEF1 virus. By continuing the hamster passages over an approximate four-year period the virus content in suckling hamster brain tissue eventually reached LD_{50} titers of $10^{-6.5}$ to $10^{-7.0}$ or greater, as determined by intracerebral titrations in white mice. The high titer secured in the suckling hamster brain tissues encouraged us to renew our attempts to establish poliomyelitis virus in developing chick embryos.

Dr. Roca-Garcia[87] established the 119th hamster passage of the MEF1 strain of poliomyelitis virus in chick embryos via the yolk sac route of inoculation. Dr. Cabasso[88] shortly thereafter confirmed Dr. Roca's findings by establishing the 131st hamster passage virus in chick embryos by the allantoic cavity route of inoculation. Since establishing the original strains in the chick embryo, we have reinvestigated frozen, infected brain tissues stored at -70°C. and have succeeded in establishing the 115th hamster passage of the MEF1 strain poliomyelitis virus in developing chick embryos.

The adapted strain of poliomyelitis may be readily maintained and propagated in the developing chick embryo. Present evidence indicates

TABLE I—MEF1 POLIOMYELITIS CHICK EMBRYO (20%) INTRACEREBRALLY IN RHESUS MONKEYS

Vaccine	*No. of Monkeys*	*LD_{50} Titer In Mice*	*Reaction*	
			Neg.	*Positive*
A 17	30	$10^{-5.00}$	28	1+(10*); 1++++(15)
A 20	10	$10^{-4.54}$	7	1+(16); 1++(9); 1++(28)
A 30	10	$10^{-3.83}$	9	1+(18)
A 40	10	$10^{-3.66}$	8	1+++(9); 1? (28)
B 10	10	$10^{-6.00}$	9	1+++(17)
B 20	10	$10^{-5.50}$	9	1+(19)
Total	80		70	10

\+ = 1 Limb Paralyzed
++ = 2 Limbs Paralyzed
+++ = 3 or 4 Limbs Paralyzed
++++ = Prostrate
* Days After Inoculation

that the major changes effected in the characteristics of the virus are induced by adaptation to the rodent host and that these characteristics remain essentially unchanged in the avian host for a considerable number of passages at least. One of the peculiar properties of the adapted MEF1 strain of poliomyelitis virus is that the chick embryo shows little, if any, signs of infection. The embryos do not die from acute infection as is so common with many other neurotropic viruses, but the great majority die at the time just prior to hatching. Maximal growth of the virus takes place apparently in the embryo itself, and the optimal time to harvest the infected tissues is on the fourth to fifth day following inoculation.[90, 91]

At present we are intensively engaged in studying the properties of the various sub-strains of the chick embryo adapted virus in relation to their safety as well as to their immunizing capacity for primates—particularly rhesus and cynomolgus monkeys and chimpanzees.

Table I illustrates some of the more pertinent data concerning some of the experimental vaccines prepared from infected chick embryo tissue and the reactions induced in rhesus monkeys inoculated intracerebrally. It must be realized, of course, that the data presented are still quite preliminary in nature. The vaccines used consisted of 20 per cent chick embryo tissue homogenized in distilled water. They are being studied for their degree of pathogenicity for rhesus monkeys inoculated intra-

TABLE II—NEUTRALIZATION INDICES OF CHIMPANZEES RECEIVING CHICK EMBRYO MEF1-17 A VIRUS

(MOUSE TITER $10^{-5.5}$)

Virus Used: Mef1 Hamster-Adapted - 131 A						
Chimpanzee	*Route of Inoculation*	*Interval in Days* 14	42	113	127*	141
Carl	5 cc Oral	12,590	2,140	31,620	11,480	12,590
Lucy	5 cc Oral	3,160	1,075	1,905	8,510	5,130
Banjo	2 cc I.M.	4,365	680	33,880	1,820	70,790
Homer	2 cc I.M.	14,790	2,140	17,380	210	1,780
Virus Titer of Test		$10^{-8.5}$	$10^{-7.33}$	$10^{-7.0}$	$10^{-6.76}$	$10^{-6.85}$

* Second 5 cc administration by oral route.

cerebrally with 0.5 ml. amounts of undiluted vaccine or serial dilutions thereof. A series of vaccines was prepared from the 17th, 20th, 30th and 40th serial passages in chick embryos derived from the 131st passage in suckling hamsters (Moyer's A series[89]). The B series of vaccines was prepared from the 10th and 20th serial chick embryo passages derived from the 127th passage in suckling hamsters (Moyer's B series[89]). It is noted that the LD_{50} titers of these vaccines, determined by intracerebral titration in mice, vary from $10^{-3.66}$ to $10^{-6.00}$. All inoculated monkeys were kept under observation for at least sixty days. Summarizing, it is seen that of a total of eighty rhesus monkeys inoculated intracerebrally, seventy remained normal, whereas ten showed varying degrees of paralysis. The monkey marked questionable on the twenty-eighth day that received vaccine A 40 showed transitory weakness lasting for only a day or so, but did not become paralyzed. It should be noted, however, that none of the paralyzed monkeys died.

It is of interest to compare these results with chick embryo propagated yellow fever vaccines, strain 17D. In a series of 200 rhesus monkeys inoculated intracerebrally with a number of yellow fever vaccine preparations, in which the vaccines showed titers ranging from 20,000 to 2,000,000 LD_{50} units for mice, 6 per cent of the monkeys died from yellow fever encephalitis, and an additional 15 per cent developed mild weakness or paralysis.[92] Thus, it would appear that the results obtained

by intracerebral inoculation of rhesus monkeys with these early poliomyelitis vaccines are quite comparable to those obtained under similar conditions with yellow fever vaccines.

Table II shows the results obtained when chimpanzees were inoculated either orally with 5 ml. each, or intramuscularly with 2 ml. each, of chick embryo vaccine A 17. None of the chimpanzees showed any ill effects following vaccination. Blood samples were collected and tested for neutralizing antibodies on the days indicated. Chick embryo vaccine A 17 showed a mouse titer of $10^{5.5}$ LD_{50}. Neutralization tests were carried out with homologous MEF1 virus of the 131st hamster passage. The dosages used for vaccination were considered to be practical quantities for human inoculation. On the 127th day post-vaccination, all four chimpanzees were revaccinated orally with 5 ml. each of the same vaccine. It is seen that the two chimpanzees initially inoculated orally gave as good neutralization titers, if not better, than those initially injected intramuscularly. The two chimpanzees initially injected intramuscularly showed a good rise in antibody titer following their oral reinoculation on the 127th day.

As stated previously, the data presented are by necessity preliminary in nature, but they are indicative of the general trend of our studies.

In summary, I wish to emphasize that no one, at the present time, can predict when a practical and satisfactory vaccine will become available for use. To attempt to make such a prediction at this time would be folly because a tremendous amount of work yet remains to be done. However, the tools for accurate, quantitative work are now available to accomplish the task. My colleagues and I are more confident than ever that eventually all three major types of poliomyelitis virus will be grown in the developing chick embryo. We believe that a living, attenuated virus vaccine, comprised of all three major types of poliomyelitis virus propagated in chick embryos, and administered by the oral route, offers the most hopeful, practical and safe procedure to follow for the immunization of children.

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MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

1953 – 1954

4:30 P.M. – Fridays

at

THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

JANUARY 8, 1954

Subject: *CURRENT CONCEPTS IN THE MANAGEMENT OF MENOPAUSE, FEMALE AND MALE*

Moderator: HOWARD C. TAYLOR, JR.—Professor and Chairman, Department of Obstetrics and Gynecology, College of Physicians & Surgeons Columbia University; Director, Obstetrical & Gynecological Service, Presbytrian Hospital

Members: FREDERICK RANDOLPH BAILEY—Associate Clinical Professor of Medicine, College of Physicians & Surgeons, Columbia University; Associate Attending Physician, Presbyterian Hospital

ROBERT S. HOTCHKISS—Professor and Chairman, Department of Urology, New York University Post-Graduate Medical School; Director of Urology, University Hospital

CHARLES M. McLANE—Associate Clinical Professor of Obstetrics & Gynecology, Cornell Medical School; Attending Obstetrician and Gynecologist, New York Hospital

S. BERNARD WORTIS—Professor of Psychiatry and Neurology, New York University College of Medicine

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HISTORICAL PERSPECTIVES OF THE PROBLEM OF ALCOHOLISM*

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THERE are alleged to be some 200,000 publications of all kinds on alcohol and alcoholism. These materials constitute a body of knowledge and opinion from which we can draw certain perspectives. Heinrich von Sybel's dictum that "the historian reports to us, not events themselves, but the impressions they have made on him," applies both in the selection and reporting that follows.

Alcohol is as ancient as plant life itself. Alcoholism, however, is only as old as man. Each has a history of its own but as their etymology suggests, they are, of course, interrelated.

The ancient history of alcohol is unknown. It is produced freely in nature and like fire was probably stumbled upon by man accidentally. Some fruit may have been left in an open bowl for a time. It fermented eventually; the yeast and bacteria normally in the air had done their work and turned sugar to alcohol, leaving a pulpy, fluid mass with a distinctive odor. Some inquisitive, hardy soul came along and, attracted by the odor, tested the first wine. At different times in the distant past, primitive men in various parts of the world, wherever there was fruit, made this same discovery. They were quick to take to it and quick to improve upon it.

They discovered that alcoholic beverages could be produced from practically any fermentable material—from fruits and berries, from flowers and honey, from the sap of trees, from milk, from almost any plant or animal substance containing carbohydrate or sugar. In the tropics they learned to use the sap of the palm tree and of the cactus; in the Far and Near East and in Europe, honey and milk from the mare and the sheep; in the New World, corn, barley, oats, wheat, sugar cane, potatoes, beans and a wide variety of other plants.

Alcoholic beverages were as important in the life of primitive man

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as they are in our own lives. They were the anodyne which permitted him to escape from the constant threats of his hostile world—cold, hunger, sickness, warfare. They became an important part of his religious and tribal life. In fact severe intoxication often accompanied religious festivals and special tribal ceremonies, although individual intoxication, apart from such ceremonies, was generally frowned upon.

Primitive man handed down to his modern heirs an alcoholic tradition that no legislation has ever succeeded in obliterating. Then as now, men drank to welcome friends and to speed them on their way. They drank to their new leaders and to the new year. They drank to brides and to grooms. They drank to the newborn and they drank to the dead. They drank to each other's health. They drank to launch ships. They drank through wars to forget their misery and defeat; they drank to celebrate victory. They drank in luxury as a symbol of their wealth and of their idleness; they drank in poverty to forget their hunger. They drank to their gods; they even drank their God's blood. And at every step along the drinking road there were those who inveighed against the excesses, those who preached temperance and prohibition.

Alcohol and the Bible

There are alleged to be more than 250 references to alcoholic beverages in the Old and New Testaments. None of these, however, suggests that alcohol is, in itself, evil. Psalm 104 is representative; it refers to "wine that maketh glad the heart of man." The 9th Chapter of the Book of Judges refers to "new wine that cheereth God and man."

Throughout the Old Testament the citations on alcohol abound with salutary symbols. The repeated references in the Book of Deuteronomy hold alcoholic beverages as one of the beneficents of God to be taken with meals in praise of the Lord.

The New Testament in the gospels, likewise speaks of wine as one of the Lord's blessings, to be cherished and preserved. The various references to Jesus indicate that he was not only *not* opposed to the use of wines but that he regarded it as permissible and as a means of enjoyment. The use of wine in the Lord's sacrament is an extension of the sacrificial and reverential use of wine by the Jews on many holy days. Both Jews and early Christians regarded wine, the product of the grape, as one of God's works, hence good.

But the excessive use of wine is strongly condemned throughout the

Bible. One of the earliest biblical condemnations of drunkenness is found in the 9th Chapter of the Book of Genesis. Upon alighting from the Ark, we are told, Noah planted a vineyard and at the first opportunity made wine from the grape and drank sufficiently to make his one of the earliest recorded lost week-ends in history. After the experiences of 377 days and nights on the Ark, it is understandable that he should seek the solace of forgetfulness in the wine! The report on this in the Book of Genesis closes with the curse that Noah laid upon his offending son and records what has become a point of view for Jews, ancient and modern, that the weakness of civilization (in this case the Canaanites) is ascribable to over-indulgence in alcoholic beverages.

There are other and numerous Old Testament condemnations of alcoholic excesses. Amos, one of the early great prophets, attacked the ladies of Samaria, calling them the kine of Bashan, charging them with exploitation of their husbands to obtain money to satisfy their demands for wine and other luxuries. Hosea cited drunkenness as one of the causes of the moral collapse of his time. Isaiah said: "Woe unto them that rise up early in the morning, that they may follow strong drink; that tarry late into the night till wine inflame them."

Perhaps the most moralistic of all of the Books of the Bible, the Book of Proverbs, which has undoubtedly served as the moral and legal basis for the extremists' credo with reference to alcoholic excesses in all times, questions and answers in its 23rd Chapter: "Who hath woe? Who hath sorrow? Who hath contentions? Who hath complaining? Who hath wounds without cause? They that tarry long at the wine; they that go to seek out mixed wine; look not thou upon the wine when it is red, when it sparkleth in the cup, when it goeth down smoothly; at the last it biteth like a serpent and stingeth like an adder. Thine eyes shall behold strange things and thy lips shall utter perverse things. Yea, thou shalt be like he that lieth down in the midst of the sea. . . . They shalt striken me, shalt thou say, and I was not hurt; they have beaten me, and I felt it not, when shall I awake? I shall seek it yet again."

There is relatively little in the Old Testament which contributes in a constructive way to the management of drinking excesses. In the 35th Chapter of Jeremiah the Rechabites advocated a return to the austere standards of the desert from whence they had originally emerged and an abandonment of the use of wine and strong drink; but this—an approach familiar to us today—was a retreat from, rather than an attack

upon, the problem of excessive drinking.

The New Testament also contains a number of warnings concerning drunkenness and other excesses. Thus the first epistle of St. Peter refers to the days when people "walked in lasciviousness, lusts, excess of wine, revelings, carousings, and abominable idolatries." In the post-apostolic period of the early Christian church, there is much evidence of a breakdown in standards of behavior amongst its leadership and a return to the practices of the "pagan society" so strongly abjured by Peter.

As a consequence, from time to time there was advocacy of total abstinence among some of the early church leaders. Its greatest vogue and influence came, however, with the major split in the Church during the Reformation. The preachments of temperance by Calvin and Luther, and those of abstinence by Wesley, the founder of Methodism, were to have a profound effect not only upon their immediate followers but upon our own time as well.

Alcohol and Ancient Cultures

The classical writers of Greece and Rome—the poets and historians, the philosophers and essayists, the physicians and commentators—also contributed greatly to our perspectives on ancient drinking customs. Athenaeus, in his classic work, *The Deipnosothists*, devoted 70 chapters to a description of 100 drinking cups of various forms and sizes made of every conceivable material—earthenware, gold, silver, wood, horn, etc. Many of these vessels, reflecting the patterns of ceremonial drinking in ancient Greece and Rome, are on exhibition in most of our great museums today.

In Greece, for example, intoxication in its ceremonial aspect is traceable back to the mythical age. The demi-god, Dionysos, is credited with the discovery of wine and its introduction into Egypt, Syria and parts of Asia. Upon his return to Greece, he was deified and celebrations and festivals called *Dionysia* were set up in his honor.

Habitual drunkenness was exceptional amongst the Greeks but intoxication at banquets and at the *Dionysia* was common. Total abstinence was rare but not unknown. There was a period in fact when the Lacedaemonians were teetotallers and imposed this practice upon their youth by compelling them to become painfully drunk, thus instilling a repugnance for alcoholic beverages. "Water drinkers," however, were generally regarded with repugnance as effeminate in the Greco-Roman cultures.

The drinking of alcoholic beverages at ancient Greek banquets and at ceremonials followed prescribed forms and was responsible in large measure for the habitual temperance of the Greeks. Unmixed wine, for example, was only drunk in small quantities at the end of dinner in a libation. Habitual drinking of undiluted wine was considered the sign of the barbarian or boor. The dilution of wine usually took place in a large *krater* or bowl and the mixture, made with hot or cold water or sometimes snow, almost always contained more water than wine. Equal proportions of wine and water were very uncommon and usually regarded as highly intoxicating.

In contrast to the relative sobriety of the Greeks, many of their writers reported the prevalence of intoxication and alcoholism amongst other nations such as the Cynthians, the Lydians, the Persians, the Carthaginians, the Iberians and the Thracians. Commentaries on the prevalence of alcoholism amongst these nations were often associated with reports of their licentiousness as well.

Roman drinking patterns also contrasted sharply with the Greeks and were marked with notorious excesses. Drinking at Roman banquets went often to the extreme of insensibility and it was common practice during the course of banquets to induce vomiting by introducing a flamingo feather into the throat of the drinker so that more drink and food could be taken. To stimulate the appetite for alcoholic beverages, moreover, raw onions and powdered pumice stone were taken.

Roman festivals, giving the populace at large an opportunity of aping their rulers' intemperate ways, were marked by widespread intoxication and, at times, by such scandalous excesses in all forms of behavior which led, finally, to a decree by the Senate forbidding any *Bacchanalia*. There were, however, other famous intoxication-marked festivals such as the feast of Flora or *Floralia* held in March and *Saturnalia* held in December.

Towards the end of the Republic inebriety was so widespread that laws were enacted in an attempt to cope with the public disorders associated with drinking excesses—including some laws directed specifically against female drinking—but, like their modern counterparts, they did little to curb the overindulgence.

Both the Greeks and the Romans distinguished between excessive drinking or intoxication and alcoholism. Pliny's description of the alcoholic is classic: "Pallor, pendulous cheeks, bloodshot eyes, tremulous hands which spill the full cup and, as an ever present penalty, sleep dis-

turbed by the furies, restlessness at night, and lastly, monstrous passions and even crimes which in their eyes have become the supreme delight. The next day wine infects their breath, and their memory is dead. This is what they call seizing life, whereas each day they lose both that day and the next."

Seneca's description quoted by Magnus Huss, who centuries later is still regarded as one of the advanced medical thinkers on the problem of alcoholism, corresponds with many clinical descriptions of the long-term, malnourished alcoholic. "The results," he wrote, "are pallor, quivering of the muscles soaked in wine, and an emaciation due to indigestion and not to hunger. Hence, uncertain and tottering gait, and constant stumbling as if they were actually drunk; hence, swelling of the skin and the distension of the belly, which has taken more than it can hold; hence, jaundiced and discolored complexion . . . and the nerves dulled and without feeling, or, on the other hand, constantly twitching. Why need I speak of the giddiness or disturbance of vision and hearing and the insidious pains in the head?" Malnutrition and possible avitaminosis, liver dysfunction and possible cirrhosis, Korsakoff's syndrome and delirium tremens mark this classic description.

The writers of ancient Greece and Rome made many observations on the relationship between excessive drinking and sexuality, prostitution, criminality and other problems. In the light of modern knowledge these ancient observations, however, are, in the main, antique and have no relationship to the facts as we know them today.

Alcohol and the Law

The early laws of the Hebrews and Romans and the later laws of the English, upon which our own legal system is based, varied a good deal with respect to irrational acts committed under the influence of alcohol. The Talmud is categorical. It says: "Drink not, and thou wilt not sin." It considers the offender, having himself produced "a temporary aberration of mind," not exempted from any infringement of the law. The Romans were more lenient. A crime committed under the influence of alcohol, *unless it was taken specifically for that purpose*—suggesting intent or premeditation—was usually punished less severely than a soberly committed crime. In this respect the English law in general followed the Hebraic tradition.

The Christian Church's attitude toward drunkenness as immoral and

sinful is rooted deeper than the asceticism of Calvin and the Protestant Reformation. As early as the seventh century A.D. the princes of the Church adopted restrictions directed specifically at the clergy whose excessive drinking had become a serious problem. The influence of the Church was so great during the Middle Ages that these ecclesiastical ordinances became, in effect, the law of the land.

The supposed evil consequences of excessive drinking do not fully account for the restrictions imposed against it in the Far Eastern religions. The English sociologist Westermarck believes that the Mohammedan prohibition, for example, "mainly arose from the Prophet's antipathy to Christianity" which had made of the wine a symbol "of the highest religious import." Other motives—the desire to prevent licentiousness, crime and other problems believed to result from drinking, and the belief that wine was physiologically polluting—are believed to have been influencing factors.

During the early Christian era up through the Middle Ages, intoxication was sharply stigmatized by the Church, hence by society, as an excess similar to gluttony, luxury and—under the Puritans—ostentation. Ecclesiastical law, first directed at the excesses of the ministry, then churchmen and churchgoers, eventually served as secular law. It was not until the 17th Century that secular law separated from church law and appeared to cope with general civilian problems of inebriety.

The first important English statute was enacted in 1606. Its preamble states: "Whereas the loathsom and odious sin of drunkenness is of late grown into common use within this realm, being the root and foundation of many other enormous sins, as bloodshed, stabbing, murder, swearing, fornication, adultery, and such like, . . . abusively wasting the good creatures of God. . . ." The penalty for each conviction under this statute was 5 shillings. The offender was "committed to the stocks for every offence, there to remain by the space of six hours," if unable to pay the fine. Blackstone interprets the time—six hours—sufficient for the offender to "have regained his senses, and not be liable to do mischief to his neighbors."

The English statute of 1606 is significant not only because it was to remain the law of England for over two-and-a-half centuries but because it served as a model for colonial as well as contemporary legislation in America.

Our colonial history is full of statutes directed against drunkenness—

generally of the disturbance-of-the-peace, violation of Blue Laws, and of profanation-of-the-Lord's Day variety. Fines, floggings, imprisonment and censure were the common penalties. Between 1643 and 1779, Connecticut, for example, passed 80 major liquor statutes of all varieties. Only two classes, those directed at drunkenness and those prohibiting the sale of liquor to Indians, minors and drunkards, are of particular interest.

Though arbitrarily selected these are some of the baseblocks upon which much of modern law relating to alcoholic beverages and alcoholism is built.

Alcoholism and Medicine

Much as we may like to think that 20th Century medicine is largely responsible for the non-moralistic, humane view of the alcoholic as a sick person and alcoholism as a medical problem, we should be aware that these views were expressed, only to be either ignored or repressed, at various times throughout history. Beginning with Hippocrates, who made cogent observations on "fever after drinking" and "acute fever, trembling of the head, particularly of the lower lip, after a while convulsions, complete delirium. . . ."—an obvious commentary on *delirium tremens*—a number of physicians added to the growing body of knowledge on alcoholism as a medical problem. It was not until the 19th Century, however, in the persons of Thomas Sutton, Thomas Trotter, Benjamin Rush and Magnus Huss, that we find the bed-rock of our current understanding and management of alcoholism.

Sutton (1767-1835) was born in England, took his medical degree at the University of Leyden in 1787 at the age of twenty and enjoyed throughout his entire professional life the esteem of colleagues and patients. While he wrote extensively on chest diseases, he is best known for his description of *delirium tremens* contained in his book, *Tracts on Delirium Tremens, on Peritonitis, and on Some Other Internal Inflammatory Affections, and the Gout*, published in 1813 by J. Moyes in London.

Thomas Trotter (1760-1832) was a general specialist in the field of alcoholism. His contribution to the literature on alcohol was probably the first comprehensive treatment of the subject. His doctor's thesis, *De Ebrietate, ejusque Effectibus in Corpus humanum*, submitted to the University of Edinburgh in 1778, was subsequently expanded (1804)

and published as the 200-page *Essay, Medical, Philosophical and Chemical, on Drunkenness.**

"I consider drunkenness," Trotter states in this *Essay*, ". . . to be a disease; produced by a remote cause, and giving birth to actions and movements in the living body, that disorder the functions of health."

The *Essay* contains many observations on etiology of current interest. On psychogenesis Trotter writes: "Again, are not habits of drunkenness more often produced by mental affections then corporeal diseases? I apprehend few people will doubt the truth of this. Does not the inebriate return to his potation rather to raise his spirits, and exhilarate the mind, than to support and strengthen the body? The diseases of body, if unattended with dejection, have no need of vinous stimulus; and three-fourths of the human race recover daily from all the stages of debility without ever having recourse to it."

Although Trotter had much to say against excessive drinking, he reflects a modern view in conceding a possible usefulness of alcohol for older people. "I am of opinion," he wrote, "that no man in health can need wine till he arrives at forty. He may then begin with two glasses in the day: at fifty he may add two more; and at sixty he may go to the length of six glasses *per diem*. . . . The stimulus of wine is favorable to advanced age."

Benjamin Rush, who contributed so much to early American medicine, medical education and psychiatry, did much to attract the medical profession to the problems of alcohol and the management of the alcoholic—all the while inveighing against alcoholic excesses.

Rush (1745-1813) received his medical education in the United States and in Europe. He was the first Professor of Chemistry in America and later became Professor of Medicine at the University of Pennsylvania. Among his numerous publications, *An Inquiry Into The Effects Of Ardent Spirits Upon The Human Body And The Mind With An Account Of The Means Of Preventing And Of The Remedies For Curing Them*, published originally in 1785, stands out as the earliest American medical contribution to the literature on alcohol. This *Inquiry* gave important impetus to the early temperance movement in the United States.

Rush was among the early medical practitioners to recognize the importance of psychiatric factors underlying excessive drinking. "Persons

* The extracts quoted here are from the American edition of 1813 published by Bradford and Read of Boston.

under the pressure of debt, disappointments in worldly pursuits, and guilt," he wrote "have sometimes sought to drown their sorrows in strong drink."

He recognized, too, the variety of treatments for alcoholism notable amongst which is the conditioned-reflex type. In principle his procedure is not vastly different from that used today. "The association of the idea of ardent spirits, with a painful or disagreeable impression upon some part of the body, has sometimes cured the love of strong drink. I once tempted a Negro man, who was habitually fond of ardent spirits, to drink some rum (which I placed in his way) and in which I had put a few grains of tartar emetic.—The tartar sickened and puked him to such a degree, that he supposed himself to be poisoned. I was much gratified by observing he could not bear the sight nor smell of spirits for two years afterwards."

A curious admixture of good medicine, sound common sense and classic temperance preachments, Dr. Rush's essay repeats a canard that has since become a bluenose favorite. Writing of a case of a Dr. Haller, he states a "notorious drunkard (was) suddenly destroyed in consequence of the vapour discharged from his stomach by belching, accidentally taking fire by coming in contact with the flame of a candle."

Finally we come to Magnus Huss. One of the earliest and most consistent temperance advocates in Sweden, Huss (1807-1890) served for several years at the Serafim Infirmary in Stockholm where he amassed a vast experience with alcoholic patients. His voluminous work, *Alcoholismus chronicus eller chronisk alkoholssjukdom*, published in 1849, serves both as the basis of the current nosology of chronic alcoholism and the source for our understanding of the alcoholic and his management. There were, of course, certain inherent weaknesses in this work. His insistence, for example, that a specific brain pathology exists in chronic alcoholism had many followers up until modern times. His psychiatric generalizations, viewed in contemporary terms, were also faulty; yet his commentaries on his case histories are singularly sound. For example, he felt that there was no definite border between the symptoms of alcoholic and non-alcoholic mental diseases. He pointed out the difficulty of determining whether the mental disorder was solely dependent upon the alcoholic excess or whether there were also other underlying factors. He also described as an outstanding characteristic of the chronic alcoholic a generalized, diffuse anxiety not attached to any

specific object. All of these points of view are inherent in much of the psychiatric as well as cross-sectional research currently being undertaken.

Summary

The Bible recognizes alcohol as a gift of God and therefore good. It condemns its abuse and trenchantly notes the tragic results of such abuse. It notes the practice of total abstinence but nowhere demands it. Thus the Bible can hardly be regarded as the legal support for contemporary moralization about drinking.

We find from the writings of the philosophers, the moralists, the encyclopedists and others of ancient Greece and Rome that both civilizations were characterized by an acceptance of the drinking of alcoholic beverages as part of their way of life; that more than a mere acceptance, there was incorporation in religious and secular ceremonials, patterns of excessive drinking; that sporadic efforts were made to cope with these excesses and the social problems associated therewith.

The history of the early laws concerning drinking referred back to the strictures laid down in the Bible to the extent that they were directed against consequences of excessive drinking—not against drinking itself. Beginning with the Reformation, however, church and secular law at various times and in various cultures were directed against drinking per se.

Medical men have a long history and interest in alcoholism and in the problems associated with it. The recognition of this condition as a medical problem, however, was not clearly stated until the 18th Century; it was not accepted generally by the profession, nor were practices initiated in terms of this premise, until relatively recent times.

THE ALCOHOL PROBLEM*

OSKAR DIETHELM

Professor of Psychiatry, Cornell University Medical College

ALCOHOLISM, although an individual health problem, must be viewed from a broad biosocial point of view. Biologic, including physiologic and pharmacologic investigations, psychologic and psychopathologic studies, and social and cultural surveys will offer pertinent information. The findings must, however, be considered in their interrelationship. As far as I am aware, only one attempt was made in the long history of the study of alcoholism to attack the problem simultaneously from the physiologic, psychologic, and environmental (sociologic and cultural anthropologic) points of view. The vision of this uniform scientific attack was offered and put into effect by the Chicago physiologist, Carlson. Unfortunately, after a few years his views were forgotten, and the problem was again attacked from the point of view of special scientific disciplines.

Alcoholism may present a problem because of acute intoxication of varying degree, with an individual response physiologically and psychologically, and more or less disturbing social behavior. This intoxication may be followed by varying degrees of "hangover" and of memory of behavior during the intoxication. Disturbing as such an intoxication may be and often demanding medical attention, the problem of great importance is not the acute intoxication nor the relatively rare delirium tremens or alcoholic psychoses but the disorder which is called chronic alcoholism. In our studies, which were supported by a grant from the National Research Council (Committee on the Study of Alcoholism),[1] we arrived at the following definitions which are suitable for clinical and investigative purposes: A patient suffers from chronic alcoholism if he uses alcohol to such an extent that it interferes with a successful life (including physical, personality and social aspects), and he is either not able to recognize this effect, or is not able to control his alcohol con-

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sumption although he knows its disastrous results. An excessive drinker is an individual who uses alcohol frequently and in large quantities and may even behave pathologically when under the influence of alcohol. He is, however, capable of overcoming the habit when he becomes aware of the necessity for it. A heavy social drinker drinks heavily during social occasions, with frequent or even regular intoxication, but the drinking does not present serious handicaps.

In these definitions terms such as addiction or compulsive drinking are avoided. From our clinical studies of a large number of patients we are in a position to state that compulsive actions in the sense of current psychopathology and psychiatry are not of significant importance in alcoholism. The same applies to the term addiction.

The results of a psychopathologic study by M. J. Sherfey[2] were significant in revealing that no special type of psychoneurosis is found in chronic alcoholism. In about one-third of our patients psychoneurotic manifestations were expressed in immature and dependent or rigid behavior. The rigid personalities might be considered somewhat compulsive but there was no indication that drinking was compulsive. Compulsion neuroses are rare; anxiety reaction more frequent. The largest group consists of asocial and psychoneurotic psychopathic personalities. Some patients are paranoid schizophrenic patients who were heavy drinkers but had been diagnosed chronic alcoholics because of their psychopathologic behavior. In a period of abstinence the true nature of the psychopathology became clear. The number of epileptics is low. Clinical, electroencephalographic, and Rorschach studies rule out epilepsy in some alcoholics who suffered from one or two convulsions.

The patient's age at the onset of alcoholism is of considerable importance. Alcoholism which starts in early adult life occurs most frequently in psychopathic personalities and in immature and dependent individuals. Heavy drinking may develop into chronic alcoholism after forty years of age in rigid persons who are confronted with increasing frustrations or who do not wish to recognize the need to curtail activities and responsibilities. Four patients whom I have studied intensively were well adjusted individuals who at forty-five to fifty in connection with prolonged life strain, developed chronic alcoholism.

Constitutional factors were investigated by Professor M. Bleuler[3] and compared later with a group in Switzerland. His studies of families of alcoholic patients revealed no evidence that alcoholic parents have a

higher incidence of epilepsy or oligophrenia in the offspring. In a majority of the alcoholics studied, endocrinologic pathology was found but was very varied. Its significance is unclear, and it was impossible to determine to what extent endocrinologic factors form a disposition to alcoholism or to emotional reactions which may play a role in alcoholism as well as in other personality disorders. The findings argue that the genetics of alcoholism are closely related to those of other psychopathologic developments. Alcoholism, therefore, is to be considered mainly as a symptom of a psychopathologic development and there is no indication that alcoholism is a special disease entity. These findings correspond closely to those of Sherfey on the clinical analysis of the patients. Bleuler's studies bring out that environment and inherited constitution cannot be separated and cannot be considered as independent etiologic factors. They support our contention that alcoholism is a biosocial problem. In treatment as well as in research into the problem, constitutional as well as environmental factors should be considered.

In order to avoid drawing conclusions from a selected group of patients, Bleuler continued his investigations on patients in Switzerland. These patients are less highly educated than those in the Payne Whitney Clinic, and on the whole from a lower economic setting, belonging largely to the skilled laborer and farmer group. The psychiatric and constitutional findings in the Swiss group corresponded well to those of our patients.

The careful study[4] of the individuals during periods of prolonged abstinence, lasting from weeks to several months, revealed interesting findings. In all our patients it was found that drinking was related to the presence of special emotions. The patient and observers are usually not aware of the considerable emotional variations which occur. Each patient presented an individual pattern of emotional reactions. The emotion of resentment was found most frequently. In a minority of the patients, anxiety and related tension were demonstrable, and occasionally tension without anxiety. In no patient did we find anxiety without tension or resentment.

In our definition anxiety is characterized by a subjective feeling of uneasiness and apprehension. No conscious threat is present but the psychodynamic factors present a danger; tension is characterized by subjective feelings of tautness, emotionally and in various muscles, and of an effort at control of one's emotions. The dynamic factors are to

some extent conscious and related to overcoming psychologic obstacles. Resentment is a sustained feeling of bitterness about an injury and a desire for revenge.

These emotions were determined in several ways. Each patient was examined by the psychiatrist (O. Diethelm) for an evaluation of emotions. If one is pursuing such studies persistently one can acquire a great deal of skill in detecting emotional reactions which are not obvious, especially after one has become acquainted with the behavioristic responses of an individual. Immediately after the psychiatric observations had been concluded a second investigator (M. F. Fleetwood) took blood from the patient's vein and subjected it to a biologic assay study. The findings of the two investigators were compared once a week and a close relationship between the psychiatric and biologic evaluations of the emotions was found to exist. These studies which have been carried out for ten years were now applied to alcoholic patients. There may be justified disagreement on the definitions which we use but the important fact is that there is close correlation between what we call emotions of anxiety, tension, and resentment and the findings in the blood.

In this biologic assay method the effect of the blood on the spontaneous contraction of the rabbit duodenum is studied. The change in the contractions can be quantified in relation to known solutions of epinephrine, norepinephrine and acetylcholine and expressed as numbers of gamma. In states of anxiety there was present an adrenergic substance which in further studies showed properties similar to norepinephrine. In the presence of tension one type of cholinergic substance was found, and with resentment another type was found.

In our study of alcoholic patients, a varying degree of resentment was found when an urge to drink was experienced. This resentment usually accumulated gradually during a few days or even weeks, not noticeable to the average observer or to the patient. When resentment reached marked intensity (25 gamma or more) the patient drank alcoholic beverages and the objective findings of resentment disappeared within an hour. These observations were made on patients who went to work from the Clinic and who broke their promise not to consume alcoholic beverages. The findings were confirmed under experimental conditions in the laboratory. In some patients tension with resentment seemed to be the essential emotion relieved by alcohol consumption. Anxiety was not found to be abolished by alcohol. In some patients re-

sentment was the outstanding emotional reaction while in others resentment was leading among other emotions. In a third group, resentment was less strong than the emotion of tension. From our studies there is no indication that the resentment of an alcoholic patient differs in any way from that of other persons. However, it seems justifiable to state that the resentment of an alcoholic patient is more promptly affected by alcohol than resentment of many other persons.

These drinking patterns existed in all of our alcoholic patients whether they were continuous or periodic drinkers. In heavy, continuous alcoholics they become, however, obvious only in periods of enforced abstinence. One gains the impression that after resorting to relief from alcohol has been started, a smaller amount of resentment induces the patient to drink than in periods of abstaining.

In control studies with drugs similar relief from tension has been observed by the administration of Tolserol (Myanesin) or sodium amytal. No drug has been found which would affect resentment in the same way as alcohol. These findings might offer an understanding of the fact that some patients can abstain from alcohol when using barbiturates while others find barbiturates of little help. Further studies along this line might clarify the relationship of alcoholism or addiction to special drugs in psychoneurotics.

Studies by M. J. Sherfey[2] have been directed toward clarifying the behavior of the patient while intoxicated. The type of emotion seems to influence the pattern of drinking. Drinking seems more likely to occur at a leisurely pace if the emotions, for example resentment and tension, are decreased promptly. When insufficient relief was obtained with a few drinks, the patients drank a considerable amount in a short time in order to become intoxicated to such a degree that they were no longer aware of their disturbing emotions. This observation was made on patients with guilt, anxiety, depressive feelings and moderate resentment. Present experiments attempt to obtain an understanding of abreaction, living-out and acting-out in alcoholic intoxication, their psychologic significance and effect on physiologic functions.

The setting in which alcoholism occurs is important. This statement refers to the personality, underlying psychopathologic disorders, physical condition and constitutional factors, social and cultural setting. Studies were carried out along various lines.

Psychologic studies which were carried out extensively on our

patients have revealed data which were significant but not referable to an elucidation of etiological factors. The Rorschach studies permitted an objective evaluation of the emotions of anxiety, tension and resentment in patients whose blood was tested with the biologic assay method. The Thematic Apperception Test offered little further understanding of psychodynamic factors in these patients who were receiving intensive dynamic psychotherapy. In none of the psychologic tests was there any indication that a special personality type predisposes to chronic alcoholism.

The physiologic factors in the large alcohol problem are insufficiently understood, and treatment is therefore severely handicapped. Theories have been proposed that we deal with pituitary-adrenal dysfunctioning and that delirium tremens is an expression of adrenal exhaustion. It has also been assumed that the constitutional make-up and biochemical findings of some alcoholics suggest hypo-adrenocorticism.

The biochemist, Roger Williams,[5] assumes nutritional defects to be of fundamental importance. He postulates that a biological individual has a specific constitutional make-up which is expressed in its biochemical functioning. In his studies on rats he found that those animals which readily developed a dependence on alcohol showed biochemical variations. These animals needed correction of nutritional defects. Dr. Williams' theory is attractive but cannot be applied to the intricate problem of human alcoholism without a great many further fundamental investigations.

It is interesting to note that large livers and liver cirrhosis have been infrequently found among the patients who were diagnosed as chronic alcoholics and more frequently among the heavy drinkers, i.e., persons who drank heavily but were able to reduce considerably or to abstain when told to do so. This observation of Sherfey is highly challenging and needs further study.[6]

The effect of alcoholism on environment is well known but the etiologic significance of social factors on alcoholism is little understood. Most of the statements found in literature are impressions gained from a relatively small group or from statistically not well selected groups. In this field the physician must be guided by studies which can be carried out by the sociologist and cultural anthropologist. There are few such studies.

Three years ago our group investigated the significance of possible

social and cultural differences in alcoholism among the Chinese in New York's Chinatown (population about 6000). A preliminary study revealed that among the Chinese the incidence of alcoholism is relatively low compared with other ethnic groups. In order to understand the sociologic factors involved it was necessary to study the broader cultural context. Sociologists, cultural anthropologists and psychiatrists formed a team of investigators. The results, presented by M. L. Barnett,[7] are that the drinking of alcoholic beverages is sanctioned but not the state of being drunk. Children grow up in a family attitude of ridicule toward the intoxicated person and if his intoxication is recurrent, of ostracism. Such behavior reflects on the drinker's whole family. The disapproval of drunkenness by the group seems to be a considerable deterrent to the development of alcoholism. The factor of social disapproval is strengthened by the strong moral obligation of the drinker to protect his family name. Drinking by women is disapproved of and habitual excessive drinking by them is rare and treated with severity. In a society where drinking except for reasons of conviviality is deplored, there is less readiness to become dependent on alcohol. Regular drinking at times other than with meals will readily lead to the reputation of being a drunkard. Among Chinese who are no longer sufficiently identified with this closely knit Chinese society, there is a larger number of chronic alcoholics but still far less than the average of the population of New York.

In the studies of our own patients a gambler's psychology was frequently found although the patient may have gambled little. It is of interest to note that gambling plays an important role among the Chinese. These observations suggest that the relationship of the gambling attitude with inhibition of its actual satisfaction to alcoholism needs further investigation. The frequency of drug addiction among these Chinese is unknown, as is also whether the satisfaction obtained through drugs decreased alcoholism. Our studies of non-Chinese drug addicts who have previously been excessive drinkers have not given us sufficient information. Another unclear point is the significance of the excessive eating which accompanies heavy drinking at social occasions. This food intake may be a deterrent to acute intoxication but may also be significant physiologically or psychologically in adversely affecting the development of chronic alcoholism.

A brief study was carried out on American Indians[8] who are alleged to be susceptible to alcohol and to react with uncontrolled behavior

when intoxicated. Furthermore, they are said to develop chronic alcoholism readily. These facts could not be ascertained in this survey study. It seems likely that the difference between the reaction of American Indians and other inhabitants of the United States is determined by sociologic and not racial factors. The behavior when intoxicated, for example, is an accepted uncontrolled behavior. There is no indication that it relates to special constitutional factors.

The example of the behavior of the Apache Indians when intoxicated illustrates well the influence of a special situation. Cultural factors and expectancy of the group are important influences. Observations along this line have been made in groups of different cultural background, e.g., aggressive and assaultive or loud and disturbing behavior whenever expected or tolerated by the group. Another point to consider is that such behavior occurs readily in adolescents and immature, psychopathic adults. Furthermore, suggestive influences can provoke it. These factors explain frequently why in certain individuals and hospitals more disturbing behavior occurs with intoxication and withdrawal of alcohol and drugs than in others. Corresponding observations can be made without alcohol or drugs, in prisons, in camps, in boarding schools. It is essential that these reactions be attributed to social and psychologic, and not to toxic, factors.

A difficult problem exists with regard to estimating the frequency of alcoholism among a population. Progress in public health, diet and the more judicious use of drugs by the physician has decreased the occurrence of alcoholic psychoses, and the number of their admissions cannot be used as a guide for an estimate of chronic alcoholism. Similar changes have occurred with regard to physical pathologic damages which may necessitate statistical reformulations (see Sherfey[6] on liver cirrhosis). The admission rate to psychiatric hospitals is also an unsatisfactory index because of the looseness of the diagnosis of chronic alcoholism. The distinction between excessive drinking and chronic alcoholism, e.g., is important but usually overlooked. It is to be hoped that the results of our studies, especially those of Sherfey, will help to clarify diagnostic terminology which in recent years has become increasingly vague.

Frequently intoxication is considered the sign of chronic alcoholism, and the observer may forget that alcoholism is not dependent on the amount alone or on the type of the alcoholic beverage. Without a good

knowledge of the patient's life and behavior, of the attitude of his society to drinking and of the cultural factors, one cannot reach a diagnosis of chronic alcoholism and plan the treatment which is indicated.

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MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

(*Continued from page 960*)

FEBRUARY 5, 1954

Subject: *CURRENT CONCEPTS IN THE MANAGEMENT OF ARTERIOSCLEROSIS*

Moderator: DAVID P. BARR—Professor of Medicine, Cornell University Medical College

MARCH 5, 1954

Subject: *CURRENT CONCEPTS IN THE MANAGEMENT OF ELECTROLYTE DISTURBANCES*

Moderator: E. HUGH LUCKEY—Director, Second (Cornell) Medical Division Bellevue Hospital

APRIL 2, 1954

Subject: *CURRENT CONCEPTS IN THE USE OF ANTIBIOTICS*

Moderator: YALE KNEELAND, JR.—Associate Professor of Medicine, Presbyterian Hospital

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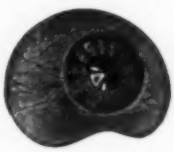

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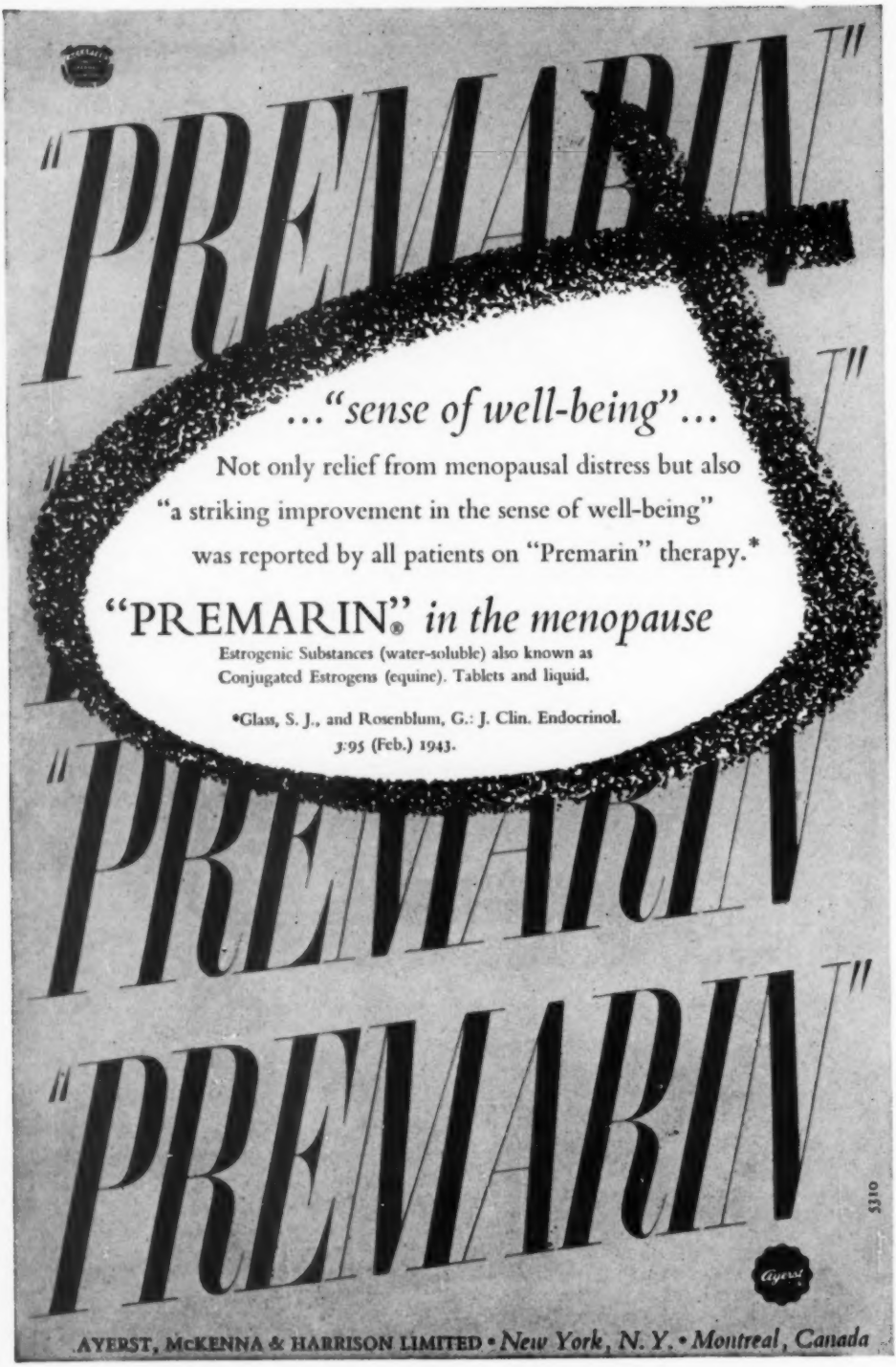
1. Rimmerman, A. B., and others: A Comparative Study of Sodium-free Salt Substitutes, Am. Pract. & Digest Treat. 2:158, 1951.
2. Fremont, R. E., and others: Postgrad. Med. 10:216, 1951.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Kountz, W. B.: Ann. Int. Med. 35:1055, 1951.

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1. Grayzel, H. G., Helmer, C. B., and Grayzel, R. W.: New York St. J. M. 53:2233, 1953.
2. Helmer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951.
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4. Turell, R.: New York St. J. M. 50:2282, 1950.

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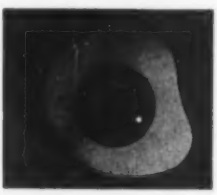

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[1]Marchisello, P. J., Prigot, Aaron, and Wright, L. T.: Am. Jour. Surg., Dec., 1952.

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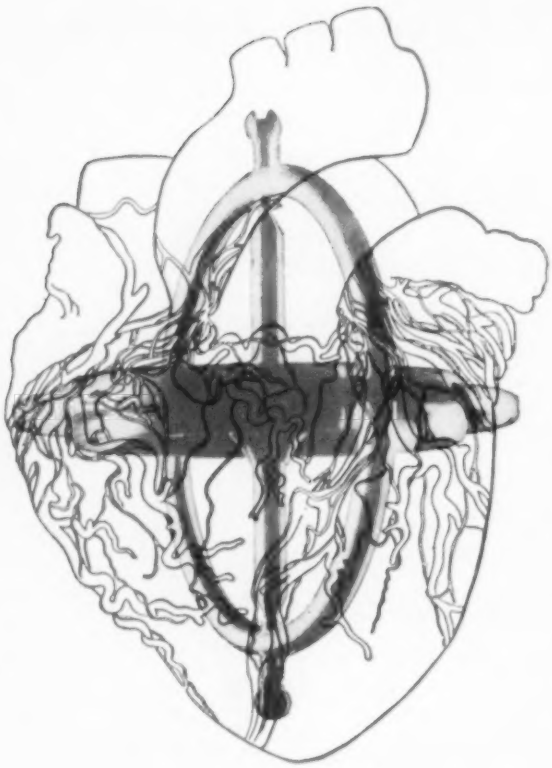

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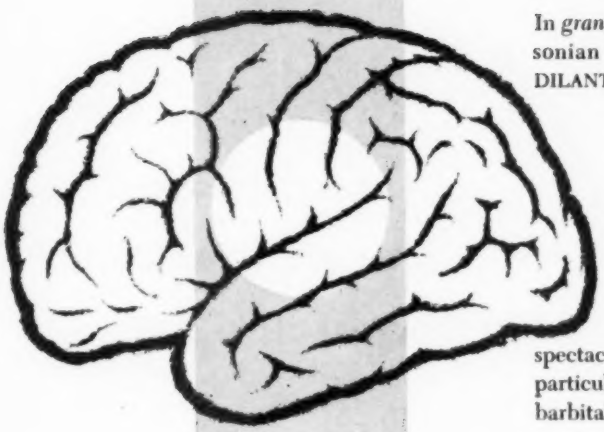

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(1) Krantz, J. C., and Carr, C. J.: The Pharmacologic Principles of Medical Practice, Baltimore, The Williams & Wilkins Company, 1949 (Reprinted 1950), p. 518. (2) *ibid*, p. 515. (3) Carter, S.: Epilepsy, in Conn, H. F.: Current Therapy 1952, Philadelphia, W. B. Saunders Company, 1952, p. 612. (4) Salter, W. T.: A Textbook of Pharmacology, Philadelphia, W. B. Saunders Company, 1952, p. 231.

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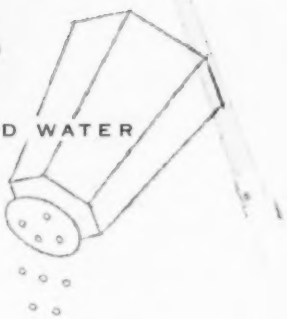

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